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BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 26 1951

EFFECT OF CORTISONE ON SURVIVAL OF SKIN HOMOGRAFTS IN RABBITS

BY

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The experiments to be described in this paper were done with two purposes in mind: (*a*) to find out if the administration of cortisone prolongs the life of skin transplanted from one rabbit to another; and (*b*) to find out in what manner the administration of cortisone influences the healing, growth, and differentiation of skin grafts as such—whether transplanted from one rabbit to another or from one part to another of the same rabbit. Cortisone is known to have a profound influence on the activity of all mesenchymal tissues, and to this family belong not only the cells that mediate immunological responses, but also those that are universally and intimately concerned in the processes of repair.

There is no acceptable evidence that the epithelium of skin grafts long survives transplantation from one human being to another, and in rabbits, mice, and guinea-pigs there is fully documented evidence that it does not. This general rule forms the baseline of the present investigation.

It is known, however, to require at least three qualifying clauses. First, it has repeatedly been shown—most recently by McIndoe and Franceschetti (1950)—that skin may be successfully interchanged between human twins of monozygotic origin, and also between mice or guinea-pigs of populations whose members, by very prolonged and strict inbreeding, have come to resemble each other almost as closely as if they were monozygotic twins (Billingham and Medawar, unpublished). It would be an almost inexplicable anomaly if this were not indeed the case. Secondly, skin may also be interchanged between twin cattle of unquestionably *dizygotic* origin (Anderson, Billingham, Lampkin, and Medawar, 1951). The majority of dizygotic cattle twins are known to have confluent foetal circulations, and to exchange haematopoietic cells which, although of genetically foreign origin, nevertheless endure into adult life (Owen, 1945). Such twins are therefore already genetical chimeras or "graft hybrids," so it is hardly surprising that they are tolerant to grafts of each other's skin. This dispensation is not known to have any bearing on the fate of homografts in rabbits, mice, or men.

The third qualification is of equally specialized import. The rule that skin cannot be interchanged between mammals of ordinary genetic diversity need only apply to *orthotopic* grafts of skin—that is, to skin grafts transplanted to positions formerly occupied by skin. Certain positions in the body (like the brain) are known to be immunologically privileged, in the sense that homografts transplanted to such positions either cannot elicit an immune response from their hosts, or, if they do so, are protected from its consequences. This exception likewise has no practical bearing on the clinical uses of homografts of skin.

The rule formulated above related only to the behaviour of the cellular constituents of skin grafts. The fibrous elements of the corium are known to be very much more resistant to effects of homoplastic grafting, although they are in due course replaced by fibres of native (that is, autogenous) origin. In certain circumstances the epithelium of skin homografts may be surreptitiously replaced by epithelium of native origin. The appearance so produced is sometimes hard to distinguish from that of a genuinely surviving homograft, and it is to this fact that claims in the literature for the occasional success of skin homografts can probably be ascribed.

A full report has already been given of the behaviour and fate of skin homografts in rabbits (Medawar, 1944, 1945, 1946a, 1946b), and these papers form the basis of several generalizations made below about the behaviour of skin grafts in normal rabbits. The only earlier work known to us which has an immediate bearing on the present is that of Whitelaw (1951), who has described the unexpectedly long survival of skin homografts in a patient under treatment with A.C.T.H. On the other hand, Baxter, Schiller, and Whiteside (1951) have described a patient on whom the administration of A.C.T.H. had no such effect.

Methods

Material.—Adult rabbits of both sexes (see Table), weighing 2.2 to 2.9 kg., were used in the experiments. Cortisone was given by a single daily subcutaneous injection of 10 mg. of a suspension of crystalline cortisone acetate ("cortone," Merck). The cortisone was provided from a generous gift made jointly to the Medical Research Council and the Nuffield Foundation by Merck & Co., Inc. The rabbits were fed *ad lib.* on the pellet Diet 18 (Bruce and Parkes, 1946), with occasional supplements of raw cabbage.

*British Empire Cancer Campaign Fellow.

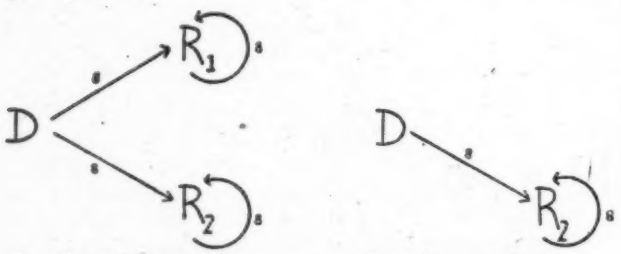
Details of Experiments

Exp.	Donor	Recipients	Autografts at 6 Days: Thickness of Surface Epithelium (mm.)	Autografts at 6 Days: Mean Mitoses per mm., ± Standard Error	Graft Bed (12 Days) Percentage of Area on Day of Operation	Homograft Survival Time (Days): First-stage Operation	Homograft Survival Time (Days): Second-stage Operation	Day of Second-stage Operation	Period of Cortisone Treatment (Days)
1	Co–4 M	*Co–3 M*	*0·010–0·020*	*1·7±0·2*	*82*	*>24 <27*	*~12*	17	*0–21*
		Co–5 M	0·050–0·095	10·6±0·6	49	7			13–32
2	Co–8 M	*Co–6 M*	*0·015–0·020*	*0·8±0·1*	*72*	*>20 <25*	*~12*	21	*0–25*
		Co–7 M	0·040–0·060	11·4±0·4	36	9			17–39
3	Co–11 F	*Co–9 F*	*0·008–0·012*	*0·3±0·1*	*63*	*27*	*~15*	18	*0–21*
		Co–10 F	0·040–0·045	5·2±0·2	61	7			14–33
4	Co–14 M	*Co–12 M*	*0·008–0·012*	*0·7±0·1*	*73*	*>21 <24*	*>9 <12*	17	*0–21*
		Co–13 M	0·040–0·045	4·6±0·4	37	7			13–31
5	Co–15 F	*Co–16 F*			*55*	*16*			*4–22*
		Co–17 M			44	9			—
6	Co–18 M	*Co–19 M*			*54*	*18*			*4–22*
		Co–20 M			44	7			—
7	Co–2 F	Co–1 F				*>15 <20*			6–20
8	Co–1 F	Co–2 F				*>40 <49*			0–40

Entries in italics relate to data obtained from rabbits under cortisone treatment. Animal Co–2 received only 5 mg. cortisone per day from the 20th day onwards.

Plan of the Experiments

Each of the principal experiments (Table, Nos. 1 to 4) made use of three rabbits: two recipients, R_1 and R_2, and their common donor D. Each experiment was done in two stages according to the following common plan (Fig. 1):



First-stage operation. Second-stage operation.

FIG. 1.

In the first stage, R_1 and R_2 each received eight skin homografts from D, and eight skin autografts as well. R_1 received the first injection of cortisone on the day before operation and was injected daily for 21–25 days thereafter. R_2 received no cortisone to begin with, and the homografts carried by it were completely destroyed within 10 days of their transplantation. R_2 being thus thoroughly immunized, daily administration of cortisone was started 13–17 days after the first operation. Four days later R_2 was made the subject of a second operation—a replica of the first, as the diagram shows, except that the eight homografts and eight autografts were transplanted to the opposite side of the body. The administration of cortisone was maintained for from 14 to 18 days after the second-stage operation. (In these apparently arbitrary choices of times we were guided by pilot experiments entered in the Table as experiments 7 and 8.)

Each such experiment made possible a controlled appraisal of the influence of cortisone on the behaviour of homografts both in a "virgin" animal, R_1, which had received no homografts before, and in an animal, R_2, which was specifically immune in the sense that it had already received and reacted against homografts from the same donor.

The adequacy of this experimental scheme is obvious except in one particular—the genetical relationship between animals R_1 and R_2.

Ideally, R_1 and R_2 should be identical twins, or should be rabbits of the same age and sex from a very highly inbred line. If cortisone were without appreciable action, the homografts transplanted in the first-stage operation from D would then be expected to live exactly as long on R_1 as on R_2.

Unfortunately, no such rabbits were available to us. Since the inheritance of the antigens controlling transplantation immunity is highly polygenic, the correct alternative was to choose three animals of great genetic disparity; in fact, in each experiment rabbits D, R_1, and R_2 were of different breeds. In practice this provided a high degree of uniformity of response, for so great was the disparity between the donors and the R_2 recipients that the homografts broke down in all of them about as fast as homografts in rabbits are ever known to do. An added advantage of this scheme was to make the test on the effect of cortisone a particularly stringent one. It must, however, be made clear that the "null hypothesis" appropriate to such a choice of animals is, not that homografts should survive as long on R_1 as on R_2, but simply that the homografts on R_2 should outlive those on R_1 as often as not. As it turned out, the effect of cortisone was so obvious as not to call for the refinements of statistical appraisal.

Besides the four experiments done in the manner just described, two others (Table, Nos. 5 and 6) were done in the same way except for (*a*) the fact that the administration of cortisone to the R_1 recipients was not started until the fourth day after operation, and (*b*) the omission of the second-stage operation on R_2. In addition, certain useful information was obtained from two pilot experiments (Table Nos. 7 and 8) of simpler but less satisfactory design. These made use of two rabbits, Co–1 and Co–2: each one received eight autografts and eight homografts from the other. Co–2 received the full dosage of cortisone (10 mg./day) for the first 20 days, beginning on the day before operation, and half this dosage for a further 20 days. Cortisone treatment was not given to Co–1 until the sixth day after operation, and was continued until the 20th day.

Operative Methods

The grafts were cut in the manner of pinch grafts from the shaved skin of the dorsum of the ears: each was a thin, flat, circular disk of skin comprising the epidermis and the full thickness of the corium, and so anatomically best described as a thin Wolfe graft. Uniformity of size was achieved by defining the

outline of each graft immediately before its removal with a sharpened cork-borer of 9 mm. bore.

The grafts were transplanted to rectangular raw areas (6 × 7 cm.) prepared by removing the skin down to the fascia overlying the panniculus carnosus muscle on one side of the chest. Each animal received eight autografts and eight homografts, evenly spaced in a 4 × 4 pattern and alternating with each other in chessboard fashion. The grafts were thus transplanted in "open" style—that is, in such a manner that each could enlarge its epithelial surface by outgrowth over the raw area separating it from its neighbour or from the margin of the operation field. Dressings were applied in the way described by Medawar (1944).

The grafts were first examined six days after operation and thereafter at three-day intervals. Biopsy specimens were removed at 6, 9, 12, and 15 days after operation, and then as often as proved necessary. Measurements of the area of the operation field and (at later inspections) of the autografts were made at each inspection. Total and differential leucocyte counts were started the day before operation, and were continued for the duration of each experiment—at first daily, and latterly, when it had proved sufficient, at two- or three-day intervals.

Operations and inspections were done under pentobarbitone sodium analgesia, supplemented, if necessary, by open ether or ethyl chloride.

Computing the Survival Time of Homografts

The breakdown of homografts is very conspicuous to the naked eye (see below), but the *accurate* timing of their survival can be based only on the microscopical evidence provided by regular graft biopsies taken over the period of breakdown. A three-day serial sampling interval was adopted, and the chosen measure of "survival time" (see Table) is that time at which the breakdown of the homograft epithelium is *just* complete. An estimate of, for example, seven days' survival is to be taken to mean that breakdown was seen to be in progress and far advanced in the six-day biopsy specimen and to be long complete in that taken at the ninth day. With most of the cortisone-treated animals, however, the process of breakdown was too vacillating and long-drawn-out to justify this sort of interpolation: an entry in the Table such as "$>24<27$ days" simply means that there was some surviving epithelium in the sample removed at the 24th day and none in that removed at the 27th, so that breakdown must have been complete at some time between the two.

The validity of this technique of serial graft sampling has been demonstrated by Medawar (1944, 1945). It turns upon (*a*) the fact that epithelial breakdown occurs simultaneously and to the same degree in all the orthotopic skin grafts transplanted on one occasion from one donor to one recipient, so that (accidents of healing apart) one homograft is truly representative of the population as a whole; and (*b*) the fact that breakdown is a progressive and never a cyclical or vacillating process in skin homografts transplanted between animals of ordinary genetic disparity. Breakdown times can therefore be reliably computed by interpolation. Even so, the discrimination between "surviving" and "dead" epithelium is a purely histological one: how accurate it can be was shown by comparing the histological diagnosis of survival with a biological test, in which homografts at various stages of breakdown were transplanted back to their original donors and so given an opportunity to recover.

Results: (1) The Healing and Histological Reorganization of Grafts and Raw Areas

(a) The Operation Field

As earlier work (Ragan, Howes, Plotz, Meyer, and Blunt, 1949) had led us to expect, cortisone conspicuously retarded the development of granulation tissue—particularly after the second-stage operation on the R_2 animals, in which treatment had started four days before the raw area forming the graft bed was prepared. The tracks of even the finest vessels of the raw surface remained visible for as long as 12 days after operation, and sections showed that the surface of the raw area consisted of the scarcely modified fascia of the graft bed as it was first prepared. Beyond the 12th day granulation tissue began to build up very slowly, and, correspondingly, the raw surface began to accept the imprint of its immediate dressing, tulle gras.

It will be clear from the entries in the Table that cortisone treatment also retarded the contracture of the operation field: column six shows, for both R_1 and R_2 animals, the area of the general graft bed at the 12th day post-operatively, expressed as a percentage of its area on the day of operation.

(b) Autografts: Healing and Histological Reorganization

The primary healing of the grafts in the cortisone-treated animals was much weaker than in their controls. After it has been in place for six days quite a brisk tug is needed to strip a normal autograft or homograft from its bed, but under cortisone treatment a six-day graft can be removed by an action more aptly described as peeling it away. Grafts peeled off at the sixth day could simply be replaced in their beds, whereupon they healed into place and continued their development without suffering a serious setback. If this is done with normal grafts of six days' standing they usually die. What seems to be a sufficient explanation of this difference will be given below.

Weakness of healing was more obvious after the second-stage operation on the R_2 animals because, by the sixth day post-operatively, they had been under cortisone treatment for 10 days. It was often found at primary inspection that the grafts had slipped or slid from the positions to which they had originally been transplanted. On the other hand, the grafts on animals Co–16 and Co–19 had healed very little less firmly than on their respective controls, presumably because the first injection of cortisone had been delayed until the fourth day post-operatively.

The administration of cortisone suppressed the traumatic inflammation that accompanies the healing process. The blood vessels and lymphatics that penetrated the grafts on cortisone-treated animals were fewer in number and individually much smaller than in their controls. Indeed, the vascular supply of the more superficial layers of the corium was conspicuously inadequate even so late as the ninth day after transplantation. The degree of proliferation of the graft epithelium makes a very sensitive measure of the adequacy of vascularization. Normal autografts and homografts have an abnormally rich blood supply at the sixth day, and the autografts retain it for six to nine days longer or even more. At the sixth day the graft epithelium displays a tremendous outburst of cellular proliferation, which subsides slowly as the vascularization returns to normal. The epidermis of the

grafts, 15–20 μ thick on first planting and containing either one or two layers of living cells, thickens to between 40 μ and 100 μ by the sixth day and acquires the differentiation into strata that is to be seen, for example, in human skin.

It is quite otherwise with grafts from the cortisone-treated animals, which at the sixth day may still be described as indolent or vegetative. As the Table shows, mitotic activity is negligible and the epidermis is no thicker than on the day of grafting (cf. Green and Ghadially, 1951).

Beyond the sixth day the difference becomes smaller, because mitotic activity in the control grafts slowly subsides and that in the cortisone-treated grafts slowly gains momentum.

The mitotic indolence of cortisone-treated grafts explains well enough why, if they are peeled off at the sixth day, they will develop without a severe setback upon replacement. There is no less reason why they should do so on this occasion than upon first grafting. A normal autograft cannot be so treated: as Peyton Rous first showed (1946), and we have repeatedly confirmed, an "active" graft with rapidly proliferating epithelium has particularly exacting metabolic requirements, and it will not withstand prolonged interruption of its blood supply.

Although the inhibitory effect of cortisone on epithelial mitosis might be due to a direct action, our own results can be equally well explained as being a secondary consequence of the effect of cortisone on the dermal blood supply. Mitotic activity in the epithelium of the graft seems to be unawakened rather than suppressed, and when in the ordinary course of growth the epithelium spreads from the graft over the surrounding raw surface it promptly thickens and shows brisk mitotic activity. Yet in this situation, because of its better blood supply, cortisone should have more immediate access to the epithelium. Moreover, the epithelium of the grafts on animals Co–16 and Co–19 was vigorously hyperplastic at the sixth and ninth days: cortisone treatment had not been started until the fourth day after grafting, so that the vascularization of the grafts was normal. This is telling evidence that the indolence of the graft epithelium in cortisone-treated animals is principally the consequence of an inadequate blood supply.

As the foregoing observations might lead one to expect, the administration of cortisone retarded the normal processes of histological reorganization within grafts. The hairs transplanted with normal grafts are thrown off in the course of the proliferation of the epithelium of the follicles, which become cystically dilated and subsequently open out widely on to the graft surface. The primordia of new hairs are normally first visible in a graft of 10 to 12 days' standing, and a fine new pelt of hairs will have pierced the graft surface by the 20th day. In grafts on the cortisone-treated animals the original hair shafts remained in place for longer and the primordia of new follicles first appeared between the 20th and 25th days. A cortisone-treated graft thus always looks more backward and immature than its normal contemporaries.

Normal autografts, if pigmented to begin with, invariably show a transient depigmentation during their proliferative phase. This is known to be causally connected with their high rate of epithelial proliferation, and is due either to the inability of epidermal melanophores to keep pace in division with their Malpighian-cell neighbours, or to the temporary diminution of pigmentary activity in rapidly dividing melanophores, or probably to both causes. Either explanation is consistent with the fact that grafts on cortisone-treated animals show little if any depigmentation and are thus more deeply pigmented than their controls. Evidently the administration of cortisone does not *inhibit* pigmentary activity, and its enhancement may be a secondary consequence of their subdued mitotic activity.

(c) Autografts: Outgrowth and the Properties of Intergraft Epithelium

By the sixth day from planting, both normal and cortisone-treated autografts had given rise to a 0.75- to 1.25-mm.-wide annulus of migratory skin epithelium, though, being at this stage poorly keratinized, it was hardly visible to the naked eye. Beyond the sixth day, outgrowth from the cortisone-treated grafts fell much behind. It often happened that outgrowth from the grafts, having extended so far as 3–4 mm. from the perimeter, made little further progress for the subsequent week or more. The perimeter of this stationary ring of epithelium was bluntly rounded, so giving the impression that the epithelium was physically unable to make progress over an unsuitable substratum.

It was the rule with cortisone-treated animals that, although vascular and fibroblastic activity and the laying down of new fibrous tissue were retarded in that part of the general graft bed that was still exposed and raw, capillary and fibroblastic proliferation developed promptly under epithelial cover. Thus the epithelium spreading from the grafts never more than briefly lay upon the almost unmodified fascia that forms the floor of the operation area, and came to be separated from it by a wide stratum of young fibrous tissue, which collagenized in the usual way, if perhaps more slowly. This effect was most conspicuous whenever epithelial migration was retarded in the way that has just been described: the building up of fibrous tissue under the stationary ring of epithelial outgrowth caused the graft to be surrounded by a raised-up, thickened tyre.

Everything that has been said of epithelial outgrowth from the grafts applies also, of course, to epithelial ingrowth from the margins of the wound. The combination of the two processes eventually provides the entire field with epithelial cover. The cover consists in part of intergraft epithelium (i.e., that which bridges the grafts) and in part of the epithelium of the grafts themselves. The intergraft epithelium is unstable, and the area it occupies slowly disappears; when the process is complete the autografts, variously changed in shape, are approximated edge to edge and to the edges of the original operation field, which is now no larger than can just accommodate them. The entire process is usually referred to as "contracture," but measurements have shown that the loss of intergraft epithelium is concurrently made good by the *expansion* of the grafts as well: expansions of area between threefold and fourfold have been recorded even in animals that have received autografts alone, so it clearly does not depend upon the alternation of autografts with homografts, as in our normal experimental design. Expanded grafts are thinner and more transparent than on first planting; during expansion the mouths of the hair follicles become separated to an extent proportional to the degree of linear magnification, and the hair pelt becomes correspondingly more sparse.

The operation field in cortisone-treated animals underwent the same sequence of changes, though so retarded as to take two or three times as long. The retardation of contracture that has already been

referred to temporarily stabilizes the intergraft epithelium. The grafts therefore remain separated for 20 days or longer by an epithelium which is flat, shiny, and (because of the development of fine cuticular fissures in an epithelium unwaxed by sebaceous secretion) of somewhat crackled or marbled appearance.

The results of sections (*b*) and (*c*) may be summarized by saying that the administration of cortisone retards the sequence of processes consequent upon grafting and the healing of raw areas without either modifying them in kind or affecting their final outcome.

(d) Graft Donor Areas

The ears of the untreated rabbits showed the expected sequence of changes. Within 24 hours they were somewhat swollen at the base and hyperaemic, and each graft donor area was seen by transmitted light to be surrounded by a halo of dilated vessels. Thick and rather nobbly scabs formed on them and their edges became puckered. The scabs could be picked off—or they dropped off—by the 10th or 12th day to reveal a fully epithelized surface, sometimes with a small central fibrous knob. The knob was larger in those donor areas from which scabs had been prematurely picked away.

The ears of cortisone-treated rabbits were at no time swollen or unduly warm, and the donor areas showed no inflammatory halation at any stage. The raw surfaces remained damp with serous exudate for one or two days until a thin, flat, parchment-like scab formed over them; their edges remained unpuckered. The scabs were attached more strongly and remained in place for longer than on the untreated animals. When epithelization was complete (we have no accurate information about its rate of progress) the donor areas proved to be uncontracted and, so far from showing any central fibrous nodules, were recessed below the plane of the surrounding skin.

(e) Striae

Typical white striae were found on the 25th day after operation in the skin surrounding the operation field on animal Co-2. Striae were found on no other rabbit.

(f) The Blood Picture

The immediate effect of the grafting operation alone is a rise in the total white cell count made up of a small increase in the number of granulocytes and a much larger increase in the number of lymphocytes (Fig. 2). When cortisone treatment is combined with the operation the number of lymphocytes, instead of rising, falls, owing to the lympholytic action of the cortisone, while the number of granulocytes increases (Fig. 3). The level of the overall white cell count varies according to the way in which these two effects balance out. The lymphocyte count remains low throughout the treatment with cortisone, and the normal blood picture is restored about 10 to 14 days after the last injection.

Results: (2) The Behaviour of Homografts

Controls

Homografts exchanged between animals of remote genetical affinity, such as those deliberately chosen for the experiments described here, elicit a rapid and violent reaction. Their primary healing is as sound as with autografts, and, like autografts, they enter a period of vigorous cellular hyperplasia. The changes they then undergo are briefly as follows. The grafts swell and harden; instead of being supple and yielding, they move as a whole, when poked, if they move at all. Meanwhile their colour changes from the delicate pink that is evidence of vascularization to brick-red and then to various shades of dirty yellow, green, or brown. The surface of the graft, instead of being white, firm, and dry, becomes damp and pasty, and the epidermis may then be peeled off to reveal the

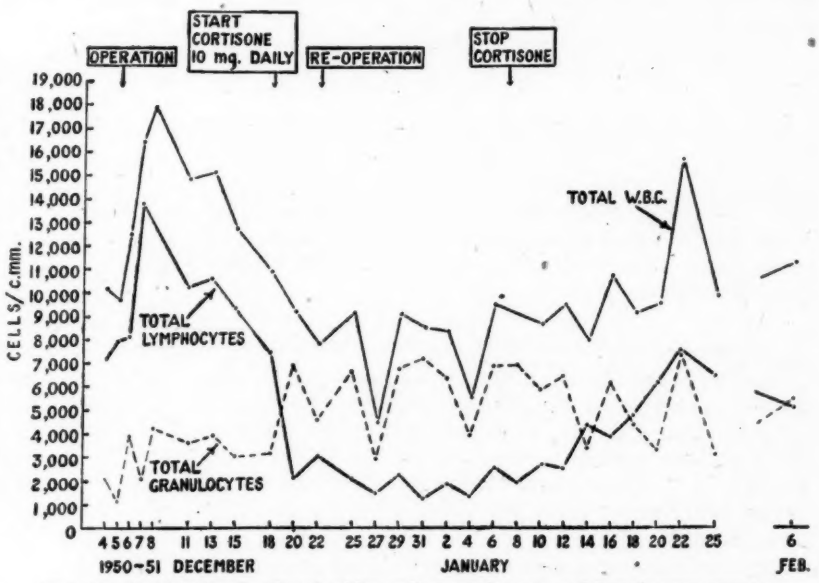


FIG. 2.—Rabbit Co-5. Total white cell, granulocyte, and lymphocyte counts.

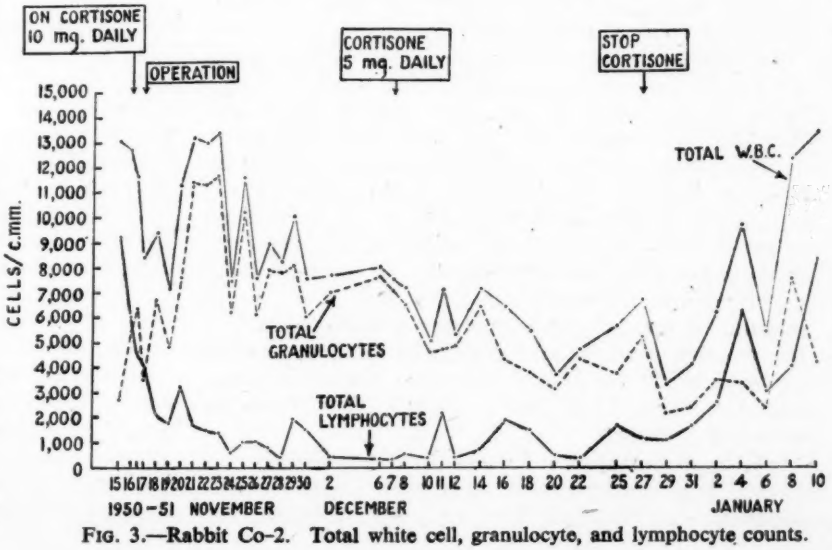


FIG. 3.—Rabbit Co-2. Total white cell, granulocyte, and lymphocyte counts.

haemorrhagic and exuding surface of the corium below. The perimeter of the graft, at first firmly united to the graft bed, becomes free all round. In the course of a few days the graft turns into a hard, dry scab; a tide of autogenous epithelium flows round it which, by biting into the deeper layers of the corium or into the surface of contact between graft and bed, gives the graft the appearance of a miniature mushroom attached to the bed by a stout fibrous stalk. When this is finally cut through by the further advance of native epithelium the mummified remains of the homograft simply drop away, leaving a small, smoothly rounded fibrous scar as evidence of its original position.

Internally, the process of breakdown is accompanied by a very violent inflammatory reaction in which the lymphocyte is the most abundant member of the invading mass of leucocytes. Destruction of the graft is accompanied by the stagnation and disruption of its grossly dilated and engorged blood vessels, the choking of lymphatics with miscellaneous cellular debris, and, finally, the breakdown of every living element in the graft, whether of native or foreign origin. In spite of the violence of the reaction, two to three days may pass between the first signs of epithelial erosion and the disappearance of the last traces of surviving epithelium. It is this latter time that has been used for computing the homograft survival time (see above).

Reference to the Table will show that no homografts in rabbits untreated with cortisone survived their transplantation for longer than nine days. (The data of Medawar (1944) gave a median survival time of 10.4 ± 1.1 days for skin homografts exchanged in about the same dosage between rabbits of a *randomly* chosen heterogeneous stock.)

Homografts in Animals Under Cortisone Treatment

The deliberate choice of animals of wide genetic disparity has subjected the effect of cortisone to a very exacting test. To translate our figures for survival times to those more appropriate to the human being (cf. Padgett, 1932; Gibson and Medawar, 1943; Baxter and Entin, 1951) they should be multiplied by a factor of three or four.

The results of the first-stage operations upon the cortisone-treated animals in experiments 1 to 4 will be considered first: in these animals the administration of cortisone began on the day before operation and continued for 21 to 25 days thereafter.

The administration of cortisone converted the acute and rapidly progressive reaction shown by the controls into a feeble, chronic reaction of delayed onset and cyclical or intermittent progress. The survival time of the homografts was prolonged by a factor of three or four (see Table). It will be seen that in animal Co–6 (as also in animals Co–16 and Co–19 of a different series) the homografts finally "died" within the term of cortisone administration, and that in no animal did the homografts live more than a few days after the last injection of the daily series. The vacillating nature of the reaction was made particularly clear by animal Co–9, in which the 21-day homograft showed a higher degree of survival than the homografts removed at the 18th and 15th days.

The inflammatory processes that accompany the normal homograft reaction were also proportionately subdued; oedematous swelling was delayed and lessened, and the lymphocytic infiltration, instead of being massive, was merely sparse and spotty. In general, the reaction was diminished in intensity without being altered in kind.

In experiments 5 and 6 the administration of cortisone began on the fourth day after operation, and in experiment 7 on the sixth. The six-day biopsy specimens from these three animals showed that a specific reaction had already begun. Nevertheless, the administration of cortisone approximately doubled their expected survival times.

The prolongation of the life of homografts by cortisone might be due to one, or a combination, of the following causes: (*a*) the homografts' diminished ability to *elicit* a reaction, as a result of the general retardation of healing, vascularization, and proliferative activity that has been seen to apply to autografts as well. That this plays an appreciable part can hardly be doubted (see below). There are several reasons why it cannot be the whole explanation, the most obvious being the prolongation of the life of the homografts on animals Co–1, Co–16, and Co–19: in these animals delay in the first administration of cortisone allowed the grafts to become as fully vascularized and as "active" as their controls. (*b*) It might be due to the partial suppression of the recipient's systemic immunological response, or (*c*) to the thwarting by cortisone of the local inflammatory and other cellular activities that accompany the breakdown of foreign epithelium and may be causally connected with it.

The second-stage operation on animals Co–5, Co–7, Co–10, and Co–13 makes possible a distinction between causes (*b*) and (*c*): these rabbits were already highly immune when cortisone treatment was started and when they received their second set of homografts. Skin homografts transplanted to an untreated rabbit that has been immunized by an earlier grafting from the same donor are known to respond in a highly modified way: epithelial proliferation is suppressed, vascular stagnation is precocious, and breakdown is very much accelerated. Upon this "normal" response must be superimposed the non-specific effect of cortisone that has already been mentioned—the retardation of healing and proliferative activity that affects autografts as well.

Homografts transplanted to pre-immunized but cortisone-treated animals remained indolent throughout their lives; they were always partially broken down by the ninth day, and in only one animal, Co–10, could it be said that there was a trace of surviving foreign epithelium at the 15th day. The response was long-drawn-out and the timing of its completion proportionately difficult and uncertain; the figures entered in column 8 of the Table are therefore much rougher approximations than those entered for the first-stage operation (column 7). Histologically, the grafts resembled "normal" second-stage homografts very closely. If some allowance is made for the delay in vascularization produced non-specifically by cortisone (that is, for reasons unconnected with the behaviour of homografts as such) then it can be fairly inferred that cortisone did not significantly prolong their lives.

Our provisional conclusion is therefore that cause (*b*) is the principal one, that cortisone prolongs the life of homografts by delaying the development of the systemic immune state rather than by preventing its local fulfilment. This is confirmed by the reduced

effectiveness of cortisone treatment in those animals (Co–1, Co–16, Co–19) in which its administration was not started until some degree of immunity had already been provoked.

The fact that cortisone prolongs the life of homografts and diminishes the inflammatory reaction that accompanies their breakdown has one rather deceptive secondary consequence: it facilitates the insidious creeping replacement of the homograft epidermis by epithelium of native origin. It was the general rule in our experiments that the fibrous elements of homografts in rabbits under cortisone treatment were progressively resurfaced by native epidermis. The appearance so produced was sometimes very difficult to distinguish by naked eye from that of a surviving homograft. In our control animals, the homografts broke down too quickly for the tide of native epithelium to have reached their margins, and the corium was in any case so poorly vascular (if vascular at all) as to make a physically unsuitable substratum for epithelial migration. Such homografts were invariably undermined, not overgrown.

Clinical Bearing

It need hardly be said that the response of the rabbit to cortisone, as we have described it above, may be very different from that of the human being. Species differences are to be expected, and our colleague Miss E. M. Sparrow finds that relatively higher doses of cortisone (5 mg./day) administered to guinea-pigs prolong the life of homografts to a somewhat less degree. With this qualification in mind we may now single out certain consequences of the administration of cortisone that may prove to have a specially direct bearing on the surgery of skin repair. The principal effect of cortisone in the experiments we have described has been to *delay* the onset and progress of certain processes mediated by mesenchymal cells; its principal benefaction in the surgery of repair is therefore likely to be to give the surgeon extra *time*, or to bring the tempo of certain naturally occurring processes under more immediate control.

Prolongation of the Life of Homografts.—The possible usefulness of this requires no comment. One of its secondary consequences is the special ease with which autogenous epithelium will overgrow (instead of undermining and throwing off) the homograft dermal fibres. Mere epithelial cover is well known to be insufficient to arrest wound contracture. It may be that epithelium is stabilized for a worth-while extra time by being caused to overgrow what becomes, in effect, a homograft of dermal fibres. To bring this about, autografts and homografts should obviously be so grafted as to lie in alternation. This is the pattern of grafting adopted in the experiments we have described and already made use of, where it is appropriate, in clinical practice (Mowlem, 1951, personal communication).

Retardation of Wound Contracture.—Fibrous contraction of the wound takes place more slowly. More time is therefore available to avoid the cosmetic difficulties due to dense scar formation.

Delay of Healing.—The weakness of the primary union of graft to bed under cortisone treatment might be thought to be a serious disability, by no means wholly compensated for by the fact that a displaced graft can be made to resume its growth and histological reorganization by merely reapposing it to its bed. One solution for this difficulty might be to allow three or four days to pass between grafting and the first administration of cortisone. It is true that four days' delay curtailed the life of homografts on rabbits (experiments 5 and 6 by contrast to experiments 1 to 4), because it allowed the building up of an effectively high degree of systemic immunity. In the common run of human surgical practice, however, the homograft reaction is slower to begin, though the rate of healing of grafts is much the same. Four days' delay between grafting and the first administration of cortisone might therefore make sound healing possible without at the same time curtailing the life of homografts.

Granulation Tissue.—The "raw area" that forms the general graft bed in cortisone-treated rabbits granulates very slowly and makes a physically poor substratum for the migratory outgrowth of epithelium.

Summary

Experiments have been designed to examine the effect of the administration of cortisone upon the healing, growth, and histological reorganization of skin autografts and upon the survival time of skin homografts in rabbits.

The daily subcutaneous administration of 10 mg. cortisone acetate to adult rabbits of either sex weakens the primary healing of grafts, delays their vascularization and the outburst of cellular proliferation consequent upon it, and retards their histological reorganization.

The contracture of graft-bearing areas is retarded by cortisone treatment, but proceeds eventually to the same degree as in untreated animals.

The administration of cortisone lengthens the life of skin homografts in rabbits by a factor of three or four.

The prolongation of the life of homografts is thought to be partly due to a non-specific reduction of the graft's own ability to elicit an immune response, but to be mainly due to the reduction of the response itself.

The survival time of homografts in rabbits already made specifically immune by an earlier grafting from the same donor is little lengthened by the administration of cortisone. It is therefore argued that cortisone affects the systemic development rather than the local fulfilment of the immune response.

[The numerical data that have been compiled, and a fuller description of our histological findings, will be included in another publication.]

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A Reuter report from Kharkov, in the Ukraine, states that 30,000 Soviet citizens are over 100 years old. "There are very few examples of such longevity in Capitalist lands," the message adds.

INHERITED IMMUNITY*

BY

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(From the Wellcome Research Laboratories, Beckenham)

Immunology is a study of resistance to infection and presupposes interactions between host and parasite. How do the defensive forces of the host overcome the pathogenic powers of bacteria, viruses, and protozoa? By what methods can susceptibility be transformed into resistance, and how can resistance be increased? I am here concerned with one aspect of the problem—namely, the transfer of resistance from mother to offspring. This important subject has only recently received the attention it deserves, and many of its phenomena still await adequate investigation.

Immunity is often subdivided into (*a*) the innate, inborn, or genetic variety, which should probably be termed non-susceptibility rather than immunity; and (*b*) immunity proper, which is always induced in response to a specific stimulus either in the subject or in his mother. The passive transference from mother to offspring (congenital immunity) is either via the placenta (or in some animal species another form of intrauterine transmission) or via the colostrum and milk.

Innate Non-susceptibility

This variety of resistance to infection should be excluded from any discussion on immunity in the strictest sense, for there may be complete non-susceptibility without previous conflict or interaction between host and parasite; nevertheless, a brief survey is indicated on account of the emphasis in this lecture on factors of inheritance. Different animal species vary in their resistance to bacterial parasites and toxins. Thus, for example, man is resistant to canine distemper and rinderpest, and the dog and cat do not get measles, poliomyelitis, typhoid fever, and cholera. Sometimes the differences between species are not complete or absolute, as in the above instances, but partial or relative. The mouse is relatively insusceptible to diphtheria toxin—relatively, that is, to the susceptibility of the guinea-pig. The dog and goat are rarely infected with tetanus, and man seldom develops avian tuberculosis. The frog is unaffected by tetanus toxin in the cold, but succumbs on warming. The fowl is naturally immune to anthrax, but on exposure to a low temperature contracts the disease and dies. These observations draw attention to a complexity in this field—namely, that the participation of inheritance in the initiation of infection is sometimes obscured by other contributory factors (exposure to cold, malnutrition, fatigue, etc.) in an individual's environment.

Genetic differences in resistance within a breed or species certainly exist (Hill, 1934), and various aspects of this difficult subject have been widely studied. Among human beings, the *relative* racial immunity of, say, the white race to tuberculosis has received much attention; it may not, however, be the result of inheritance of an acquired characteristic, but rather a consequence of the elimination of susceptible persons for generations, with the result that the hardier survivors beget children less susceptible to the disease. In the laboratory, selective breeding has been used to increase or lower the average resistance (to an infection) of a suitable strain of rats, mice, or other experimental animals. On the whole this work has not been very satisfactory, and there have been sources of error. Carriers may infect young animals, and thus influence their immunity state. In other experiments the results may have been vitiated by the passing on to some young animals of a temporary passive immunity, likely to mislead the unwary into the belief that a more resistant strain of animal was in process of development. Then again, as Hill, Hatswell, and Topley (1940) have shown, resistance may be acquired to one aspect of the attack of an organism—for example, the endotoxin of *Salm. typhi-murium*—without any increase in resistance to the one thing that really matters—namely, infection with the living bacillus.

Hereditary differences in the immunizability of guinea-pigs have been studied by Scheibel (1943), who was able to segregate a guinea-pig population, by selection and inbreeding, into a good strain and a poor strain of diphtheria antitoxin producers.

It is not surprising that we have not been able to influence to any extent the differences in susceptibility which exist between species or between individuals of the same species. We do not understand the mechanism at work, which must surely be a prerequisite for success. Variations in genetic pattern have been suggested, and all would agree that for an animal to be susceptible there must be mutual affinity between parasitic products and the body cells. Bigger puts it very aptly: the key (the bacterial or other parasitic product) must fit the lock (the cell protoplasm).

Congenital Passive Immunity

Passive immunity of homologous type is transmitted from mother to offspring (*a*) in man, apes, and rodents predominantly via the placenta (or other intrauterine mechanism); and (*b*) in sheep, goats, cows, horses, and pigs via the colostrum, which may be rich in antibody and is absorbed rapidly by the newborn animal. The alimentary tract of the young animal has high absorptive power and no digestive ferments, and these factors may explain the success of immunization by ingestion in certain animal species when placental transmission of antibodies is absent or negligible. A few hours after the first feed the titre of the serum of the young animal may equal or exceed that of the mother.

The relative importance of the placenta and the colostrum in transmission was believed to be due to the number of layers of tissue between the maternal and foetal circulations. The following summary was compiled by Mason, Dalling, and Gordon (1930) from the data then available:

	Layers of Tissue Between Maternal and Foetal Circulation	Placental Transmission	Importance of Colostrum
Pig	5	−	+++
Ruminants	4	−	+++
Carnivores	2	±	+
Rodent, ape, man	1	+++	±

Since the 1939–45 war a number of papers on the transmission of antibodies in the horse have been published by French workers at the Pasteur Institute (see, for example, Lemétayer, Nicol, Girard, Corvazier, and Cheyroux, 1949).

*A lecture given at the London School of Hygiene on November 9, 1950, in the course on "The Scientific Basis of Medicine" arranged by the British Postgraduate Medical Federation.

Brambell and various collaborators (1946–50) have been studying intensively the mechanism of immunization of the mammalian embryo; their results have a bearing on the current theory of placental permeability. First, working with the rabbit, they have shown by electrophoresis and the ultracentrifuge that albumin, alpha, beta, and gamma globulins, and fibrinogen are present in the yolk-sac fluid of seven- and eight-day embryos. The proportions of these plasma proteins are similar to those in the maternal plasma. Secondly, agglutinin for *Brucella abortus* passes freely from the mother into the yolk-sac cavity before the allantochorionic placenta is formed. This finding signifies that agglutinins can, and do, pass from mother to foetus by a route other than the allantochorionic placenta.

Brambell considers that the yolk-sac provides a possible route into the embryo for maternal globulins in other rodents also, but he makes the important additional point that in man it is precluded on morphological grounds from replacing placental transmission.

Protein Chemistry.—At this stage it is useful to consider the bearing of protein chemistry on immunity findings in certain of the animal species shown in the above table. On analysing human maternal and foetal plasmas by electrophoresis, Longsworth, Curtis, and Pembroke (1945) found that the concentrations of total globulin were lower in the newborn than in the mother. There was, however, a relative and absolute increase in the gamma globulin in cord serum, an observation which can be correlated with the higher titres of certain antibodies in cord blood than in maternal blood. The gamma globulin is, of course, a main protein fraction containing antibacterial substances such as typhoid agglutinins, antibodies to the viruses of measles, mumps, influenza, and many other infections, and to some extent antitoxins.

When we compare the serum of man with that of ruminants we find that the gamma globulin is absent in the latter at birth, and so, in accordance with expectations, are various antibodies. However, as we have seen, ingestion of colostrum rapidly makes good the deficiency. There is more globulin in colostrum (including human) than in the later milk, and this is connected with the building-up in the colostrum of antibodies of all kinds. Before or immediately after birth the colostrum titres of antibodies approach or may be much greater than the serum titres of the mother. Later the colostrum and milk titres fall rapidly (Mason, Dalling, and Gordon, 1930; Sugg, 1935). Marrack (1947) has given a useful review of the literature of antibodies in milk.

The gamma globulin in the serum of different animal species shows a fall in the early weeks of life, until the level is lower than that of the same fraction in the mother; the data accord with the immunological evidence of falls in circulating antibodies during that period.

Transmission of Antigens.—If antigens could be transmitted from parent to offspring this would have a profound influence on immunity mechanisms. However, there is no clear evidence that the ordinary bacterial and virus antigens are ever transmitted either via the intact placenta or in the colostrum and milk. The Rh antigen which produces isoimmunization of the mother is believed to pass the placental barrier from foetus to mother on account of some local damage of the villi: the significance and consequences of this accident are discussed later.

Formation of Antibodies.—A predominant part in the production of immune globulins is played by the local lymph nodes. Fat and muscle are also of subsidiary importance—not necessarily the fat and muscle cells, but possibly the granulation tissue formed in these organs (Oakley, Warrack, and Batty, 1949). Burnet and Fenner (1949) have reviewed the mechanism of antibody synthesis from normal globulins.

Immunity to Various Infections and its Acquirement

As we have seen, the mechanism of placental transmission of antibodies is so efficient in man that the colostrum and milk play a negligible and subsidiary part. From the immunological side, breast-feeding is not apparently of fundamental importance to the human infant; there is no evidence that breast-fed babies are better protected against the exanthemata than are artificially fed infants.

The routes of transference of antibodies from mother to offspring having been considered, what is the immunity state of the young animal, and especially the human infant, to various infections?

Antitoxic Immunity

Diphtheria

In the human species, if homologous antitoxin is present in the mother's serum it is transferred to her offspring almost entirely via the placenta. Barr, Glenny, and Randall (1949) have made certain observations, which should influence the practice of immunization. They began with a study of the "concentration of diphtheria antitoxin in cord blood and rate of loss in babies": a noteworthy finding was that the antitoxin content of cord blood was as a rule appreciably *higher* than that of the mother's blood taken during labour or after delivery. Secondly, interesting data were obtained about the rate of loss. They state: "There is a steady logarithmic rate of loss of antitoxin in babies which averages 13.9% per week, falling from an initial average value 36.9% below that of the cord blood. The average antitoxin content of the serum of babies 10 days old is half that of the cord blood; subsequently the babies lose half their antitoxin every 4½ weeks."

Vahlquist (1949) and Barr, Glenny, and Randall (1950) independently found that passive titres above a certain level caused serious interference with active immunization as carried out by them.

Barr, Glenny, and I (1951) have completed a survey of diphtheria antitoxin in the cord blood of infants in various towns; large differences have been detected, and it is obvious that the immunity state of very many adults in this country is dangerously low.

The active immunization of mothers during pregnancy is contraindicated when the course is given for the benefit of their offspring (Di Sant' Agnese, 1949; Barr, Glenny, and Randall, 1950), mainly because it enforces postponement of active immunization of infants for a variable number of months—possibly till the second year of life.

Further detailed consideration of such important subjects as (*a*) the optimum time for routine immunization of children; (*b*) diphtheria in the first year of life (many cases and local epidemics have been reported in neonatal and nursing infants); and (*c*) the effect of the practical disappearance of diphtheria in many areas on the passive protection of the newborn infant, would hardly be justified in the present limited survey. I have discussed the literature of certain aspects of these matters elsewhere (Parish, 1949). Two points arise, however—namely, the interesting "resistance" of the mucous membranes and skin of young babies, and, secondly, the state of development of the antibody-producing mechanism in early life.

The mucous membranes of the young infant seem to be more resistant to infection than are those of the

older subject, and this may be one factor in the lower incidence of diphtheria in babies. In many infants the Schick test is negative even when there is little antitoxin in the serum; moreover, when it is positive the reaction tends to be smaller than in older persons (Wright and Clark, 1946). (The term "anergy" has been given to the extreme form of lessened skin reactivity). It is not surprising that the evidence from Schick readings in the early months of life has often been misinterpreted.

The literature is conflicting about the state of development of the antibody-producing mechanism of the newborn infant. Many have held that it is not fully developed, so that, for example, the diphtheria antitoxin response in young infants is not as satisfactory as in older children. However, older children, like older horses, owing to the possible development of primary immunity from the stimuli of sub-infecting doses of toxigenic bacilli, would be expected to respond better than the very young. The responses of young infants may also be "blanketed" by antibody acquired passively from their mothers; when this is absent, infants' cells can and do respond well to specific stimuli (Vahlquist, 1949; Barr, Glenny, and Randall, 1950).

The passive antitoxin so far mentioned in this discussion has been homologous in type. As Hartley (1948) has shown, heterologous antitoxin given to animals or to women in the late stages of pregnancy behaves differently. Horse diphtheria antitoxin given to a woman for therapeutic purposes is *not* transferred to her infant, who may contract diphtheria from her and require independent treatment with antitoxin. After this observation, Hartley carried out experimental studies in pregnant guinea-pigs. Unconcentrated (native) guinea-pig antitoxin and guinea-pig antitoxin concentrated with ammonium sulphate passed through the placenta readily. Unconcentrated horse serum and horse serum concentrated with ammonium sulphate passed through the placenta less well than the homologous products. The really unexpected finding was that refined pepsin-treated antitoxin, homologous as well as heterologous, was recognized in the serum of the newborn young in only minimal concentrations or not at all. The explanation of this failure in transmission is not obvious. It is unrelated to the size of the molecule, since the antitoxic molecule of refined serum is about half that of untreated serum; theoretically, this should facilitate its passage through the placental barrier rather than act as an impediment.

Other Infections

Staphylococcal Infections.—Murray, Calman, and Lepine (1950) have estimated the concentration of antibody to staphylococcal α-haemolysin in blood samples from the mother during labour, the cord, and also the infant in the first day of life. As had been shown previously for diphtheria antitoxin, the titres of the cord blood and the infant's blood were in the great majority of cases higher than those of the mother's blood. Anti-α-haemolysin is only one of the antibodies to staphylococci. While a passive immunity to certain specific antigens (toxins) may be transferred, the immunity state which is inherited may be far from complete; the newborn infant tends to have a poor resistance to bacterial invasiveness. Staphylococcal skin lesions, sometimes in association with conjunctivitis, have often been reported in maternity hospitals and elsewhere. Everything possible should be done to prevent cross-infection. The maintenance of good nutrition of mothers during pregnancy is also important, as this will assist local tissue immunity to staphylococci and other bacteria.

Scarlet Fever.—The serum of newly born infants has similar blanching power to that of their parents, indicating that the antitoxic levels correspond. Another interesting observation is that the skin of the newborn is usually insensitive to Dick toxin in considerable doses; skin sensitivity appears later (Cooke, Keith, and Ermatinger, 1927; Cooke, Brinkerhoff, and Woods, 1928; Cooke, Ermatinger, and Brinkerhoff, 1928). A scarlet-fever rash is also extremely rare in young babies. The "anergy" observed with diphtheria toxin has thus been noted with haemolytic streptococcal toxin also.

Tetanus.—Natural antibody to tetanus does not occur. Therefore mothers as a rule have no circulating antitoxin in their serum to pass on to their offspring, and interference with active immunization by congenital antibodies is not a practical problem at the present time as it is in diphtheria. However, it is worth remembering that women who have served in the Forces and been actively immunized with tetanus toxoid may have considerable amounts of antitoxin in their serum even after many years. Further, women attending summer camps in the U.S.A. may receive a course of toxoid. The congenital antibodies which the infants of such mothers may receive via the placenta may cause difficulty when active immunization is attempted in the early years of life. Cooke and her associates (1948) studied 284 healthy infants between 1 and 14 months old, and found that the mechanism for the production of tetanus antitoxin was as well developed in the early months of life as later.

Gas Gangrene.—As Mason, Dalling, and Gordon (1930) have shown, antibodies to *Clostridium welchii* type B—the lamb dysentery bacillus—are transmitted to sheep via the colostrum. They have also shown that a similar mechanism of transmission is at work in the cow, bitch, and mare. It is now well established that lamb dysentery can be controlled in the field by active immunization of ewes. In the human species, *Cl. welchii* antitoxins would presumably be transmitted via the placenta in the same way as other antitoxins.

Antibacterial Immunity

Whooping-cough.—Antibodies such as agglutinins and complement-fixing substances are passed on from mother to child via the placenta. If a woman is immunized during the last three months of pregnancy, the cord blood serum contains antibodies, usually in somewhat lower amounts than the mother's serum (Adams, Kimball, and Adams, 1947). Antibodies are also present in the colostrum, but, as in the case of diphtheria and tetanus, their significance is probably negligible. Agglutinins, etc., are not a measure of protection against pertussis, although their development indicates an immunological response to a specific stimulus. That is all one can say, for unfortunately there is little evidence that immunity in the sense of lowered susceptibility is transferred from mother to offspring. Whooping-cough in the newborn has been described by Keizer (1948). The infection is well known to be dangerous in the first year of life; the younger the child the more are lung complications to be feared. Early active immunization is important, therefore, and fortunately it is a safe and practical procedure, though success is not possible in all infants (Waddell and L'Engle, 1946).

Tuberculosis.—No immunity appears to be inherited; on the contrary, the child is more susceptible than the adult, and the younger the patient the greater the risk of infection. According to Blacklock (1947), the source of infection in a series of 144 cases of tuberculous meningitis was the mother in 44%, the explanation of this high figure being the close contact during nursing, dressing, fondling, etc.

"White Scours" in Calves.—The diarrhoea of young calves is often associated with *Bact. coli*, and it has been shown that any antibodies present in the colostrum are transferred to the young. We have seen that active immunization of the ewe has been used to good purpose in the campaign against lamb dysentery. Unlike lamb dysentery, however, "white scours" cannot be controlled in practice by active immunization of the mother, owing to the variable antigenicity of different strains of *Bact. coli* (Lovell, 1950). It is to illustrate this type of difficulty that I have mentioned this common disease of veterinary importance.

Leprosy.—Some immunity may be carried over from parents to children. When it is lost there is a phase of increased susceptibility, when child contacts of the disease are more prone than adults to contract the infection.

Syphilis.—Unless the infection is virulent, signs of inherited syphilis may not be well developed before the third week. Complement-fixing antibodies have been studied. If the infant is apparently healthy, a positive Wassermann reaction does not necessarily imply that infection has been inherited. A negative reaction does not necessarily signify that the infant is safe; repeated serological tests are indicated (Macfarlane, 1950). In addition to complement-fixing antibodies, the evidence for a partial (and very uncertain) "antibacterial" immunity to syphilis in rabbits and man is discussed by Wilson and Miles (1946).

Antiviral Immunity

Smallpox.—Viral antibodies are said to be equally high in maternal and infant bloods. Unsuccessful vaccination in the newborn may be due partly to these antibodies and partly to the skin refractoriness or "anergy," which I have also mentioned in connexion with the Schick and Dick tests. Antibodies and "anergy" usually disappear in three to four months—an arbitrary period, as exact estimations are not practicable. It should be noted that "anergy" has nothing to do with immunity. The usual recommendation is that infants should be vaccinated at four to six months, except in the face of an epidemic, when vaccinations should be carried out irrespective of age.

Measles.—The risk to the infant depends entirely on whether the mother has had measles. If she has, a passive immunity may be assumed which lasts for, say, four to six months. In the very few instances in which there is no history of maternal measles full susceptibility of the offspring is likely, although cases of measles in infants under 6 months of age are actually very rare. Thereafter the disease enters on its most dangerous phase, most deaths occurring between the ages of 6 months and 3 years.

Poliomyelitis.—In connexion with this disease we should recall that cases which can be diagnosed clinically are only a small percentage of the total of persons infected with the prevalent type of virus. When mothers have neutralizing antibodies to a virus of poliomyelitis in their serum, as they often have, the same amounts are said to be present in the serum of their children at birth. As with the antitoxins, antibodies to viruses are transient and "disappear when the child is between 6 months and 2 years of age" (*J. Amer. med. Ass.*, 1950, **142**, 525). In spite of the confident statements of some writers, only preliminary investigations have so far been made, and much further epidemiological and laboratory work is indicated. Baskin, Soule, and Mills (1950) have reported two cases of poliomyelitis in the newborn, and discuss whether the illness in one of these cases developed after an incubation period of only three and a half days or resulted from an intrauterine infection. At all events it follows from both cases that newborn infants are not invariably immune to poliomyelitis.

Immunity to Protozoal Infection

Malaria.—Congenital malaria is occasionally encountered (Jones, 1950) and has aroused much interest (*British Medical Journal*, 1950, **2**, 451). Jones had drawn attention to the notable contrast between (*a*) hyperimmune indigenous populations, among whom infection of the placenta is very common but congenital malaria very exceptional, and (*b*) relatively non-immune, non-indigenous persons, among whom infection of the placenta is very rare but congenital malaria relatively less rare. He suggests that, as immunity to malaria increases, infection of the placenta becomes more frequent; at the same time the infected placenta becomes a more efficient barrier to the transmission of parasites, and consequently the incidence of congenital malaria falls. Peel and van Hoof (1948) have suggested that the numerous phagocytes observed in the placentae of natives might be expected to impede placental transmission of the parasite; this suggestion harmonizes with Jones's views.

Congenital acquirement plays a part in conferring increased susceptibility or resistance to a number of micro-organisms and toxins other than those discussed, and also to carcinogenic chemicals; the infections dealt with above are a representative and important selection.

There are many contributory factors in an individual's environment which tend to obscure the participation of heredity. Our knowledge, particularly of innate non-susceptibility, is incomplete, and more is in fact known about the hereditary transmission of certain diseases through the agency of abnormal genes than about the factors that determine resistance.

The Transmission of Iso-agglutinins

Antibodies are not invariably beneficial, and their interaction with the corresponding antigens may cause disease or death of the foetus. One aspect of this problem is the transmission of Rh antibodies.

The mother of a child with erythroblastosis foetalis, or haemolytic disease of the newborn, is nearly always Rh-negative. The father and the child itself are Rh-positive. The mechanism by which the disease is produced appears to be that small quantities of foetal blood containing the Rh antigen escape through the placenta (which may show a local lesion of the villi) into the maternal circulation and produce iso-immunization of the mother. Antibodies are produced in her serum, which pass back into the foetal circulation.

Antigen–antibody reactions then take place between these antibodies and the Rh substance in the infant's red cells and possibly other tissue cells. This is one instance in which the permeability of the placenta to antibodies is certainly not a protective mechanism.

The disease may take various forms. Apart from intrauterine death, occurring usually during the last three months of pregnancy, and leading to stillbirths, infants born alive may show various degrees of anaemia and jaundice, consideration of which is outside the scope of this lecture. However, in view of the attention I have given to placental and colostral transmission of antibodies, the following observations are interesting and relevant.

The infant is not necessarily affected when Rh antibodies are present in the maternal serum.

The first child of a marriage is seldom affected unless the Rh-negative mother has received a transfusion of Rh-positive blood. With this exception, the disease rarely appears till the second or third pregnancy.

What part does colostrum and milk play in erythroblastosis, and is breast-feeding permissible? Rh antibodies can easily be demonstrated in the breast milk of mothers whose blood serum contains antibodies, and who have borne erythroblastotic babies. Although these antibodies are not readily destroyed in the stomach of infants, there is no evidence that they are readily absorbed into the blood stream (Cathie, 1947). The consensus of expert opinion at present is that infants with haemolytic disease need not be weaned because Rh antibodies are present in the maternal milk.

Iso-immunization of pregnancy, leading to jaundice or other manifestations of the syndrome of haemolytic disease, has been observed in horses, mules, and dogs, and further work is in progress (Coombs, 1950). Many problems still await elucidation, or are insufficiently understood—for example, the factors influencing the extent and rapidity of the haemolysis and the degree of jaundice resulting. The capacity for cell regeneration and the rate of haemolysis vary considerably from case to case and influence the degree of anaemia. Holman (1950) says: "Of the other variables which make the understanding of this disease difficult, the most interesting is the occasional variation from pregnancy to pregnancy where one sees infants with the same Rh gene subject to the same or more powerful antibodies, and yet the later pregnancy will sometimes be less severely affected."

In connexion with the A, B, and O blood groups, death of the embryo in very early pregnancy may be due to antigen–antibody interaction—yet another example of misadventure from the inheritance of antibodies.

Summary

Different animal species show an inborn racial immunity, or non-susceptibility, to various infecting agents.

Congenital immunity is acquired by the passive transfer of antibodies made in the mother to her offspring, either via the placenta (or other form of intrauterine transmission) or via the colostrum.

There is a correlation between the transfer of antibodies and that of gamma globulin.

Transference through the placenta, after passive immunization of the mother, occurs more readily with homologous than with heterologous antitoxins.

It is widely held that the active responses of very young animals to injected antigens are relatively unsatisfactory owing to immaturity of the antibody-producing mechanism. However, the young human infant responds well to an injection of diphtheria or tetanus toxoid, provided that the level of the corresponding antitoxin transferred from the actively immunized mother is so low as not to cause interference.

Congenital immunity to a representative variety of micro-organisms and toxins has been considered in the main sections of this lecture. In a concluding section, a brief account has been given of certain aspects of Rh-antigen–antibody interactions, and it is shown that the transmission of antibodies is not invariably beneficial.

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The *Manchester Guardian* reports that the Committee of Inquiry into Weights and Measures Legislation recommends that the Government should take steps, in co-operation with the Commonwealth and United States, to abolish the Imperial system of measurement in favour of the complete adoption of the metric system over a period of about twenty years. Sir Hartley Shawcross, in a written reply in the Commons, said that there were many difficulties, and pointed out that the Government was not in any way committed to adopting the recommendation.

HYPOTHYROIDISM IN CHILDHOOD*

BY

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Conditions resulting from deficiency of the thyroid gland form the most important group of endocrine disorders in childhood because they are the most common and because they are the most amenable to treatment. They hold a place of importance also in medical history, for their relation to the thyroid gland was recognized long before that of myxoedema.

Nomenclature and Aetiology

The word "cretinism" is used rather loosely in referring to all types of hypothyroidism in children. We may perhaps qualify it by prefacing the word "sporadic" or "endemic"; and we sometimes speak of "juvenile myxoedema." Some regard these terms as variants of the same condition, but authorities such as McCarrison (1917), Gardiner-Hill (1937), Zondek (1944), and Means (1948) consider that sporadic and endemic cretinism are of quite distinct aetiology. Certainly, broad distinctions can be made between the two types. Endemic cretinism is the product of generations of goitrous families. The cause of sporadic cretinism is less definite. Affected children are the offspring of healthy parents. The mother in some cases may have a small goitre, but signs of myxoedema are not present. In sporadic cases it is probable that there is a developmental defect, whereby the thyroid gland is absent or small. In three infants who died at 3–3½ months, the gland was completely absent; in a fourth who died at 8 months, the gland was small and thin, and was situated over the trachea below the cricoid cartilage.

Some acute infection in the mother during pregnancy may, by transplacental infection, lead to inflammatory changes and fibrosis of the foetal thyroid. We have records of a post-mortem examination on a premature baby whose mother had an attack of influenza shortly before its birth at the 34th week. The main finding was a pericholangitic biliary cirrhosis, but inflammatory changes were found also in the thyroid. There was a marked increase in fibrous tissue, and the vesicles were small and lined by cubical epithelium. Only a few vesicles contained a pale granular and often vacuolated colloid, and most were filled with desquamated epithelium cells. In similar circumstances infants may survive with thyroid glands of varying degrees of efficiency, and herein may lie some explanation of the differences in the time of onset or in the severity of the deficiency. Post-natal infection may also be a cause of sporadic cretinism. It is certainly true that in some cases the onset of signs dates from an acute infection such as measles or pneumonia.

Since the use of thiouracil in the treatment of hyperthyroidism, there arises the danger of congenital goitre with hypothyroidism being added to the list of iatrogenic diseases. The drug can pass through the placenta, and it is also excreted in the milk. It seems, however, that in these circumstances the changes are reversible and the infant will recover spontaneously if breast-feeding is avoided.

*Abbreviated from the Ingleby Lectures delivered at the Medical School, Birmingham University, on May 25 and June 1, 1950.

The important disadvantage in the general use of the term "cretinism" is that it fails to denote the fact that a great variety of clinical pictures exist. I would prefer the terms "congenital hypothyroidism," "post-infective hypothyroidism," and "endemic cretinism."

Diagnosis

Before trying to describe these three types of case, I must refer to the question of diagnosis. Diagnosis of hypothyroidism depends primarily on the appearance of the patient and on the change which takes place after giving thyroid extract. That does not mean to imply that they all look exactly alike. Mongols, with whom cretins are so often confused, are as like each other as peas in a pod, but that is not true of cretins. These resemble each other only as much as do members of the same family.

Diagnosis is confirmed by *x*-ray examination for signs of delay in skeletal development, by estimation of the cholesterol and the phosphatase levels of the blood, and by the electrocardiogram. Signs of delay in ossification are always present, the blood cholesterol is usually high, the phosphatase is usually low, and the electrocardiogram almost invariably shows some characteristic change. Improvement after thyroid medication is revealed in these indices as well as in the general appearance, and periodic examinations are useful for assessing progress and the adequacy of treatment.

Classification of Cases

My observations are based on a study of 30 patients whose present ages range from 18 months to 20 years; 25 are now more than 4 years old. I have seen 28 of them at more or less regular intervals since their first attendance and two have reappeared after an interval of several years. In addition, I shall refer to four cases of which I have now lost sight, because they present features of special interest, and to four others—one child of 10 years and three women aged 25, 27, and 38 years—whom I have seen on one occasion only. Lastly, four female infants were examined at necropsy. This makes a total of 42 cases (31 female, 11 male). I have classified them into three groups.

Group I: Congenital Hypothyroidism

In this group were 24 cases: 19 (13 female and 6 male) from those successfully followed up, the 4 female infants who died, and one woman (now aged 25) who was seen on one occasion only.

These are cases in which there is a developmental defect of the thyroid gland, or in which the gland has been damaged *in utero* as a result of some maternal infection. Normally the foetal thyroid becomes sufficiently active about the third month (Clement Smith, 1945) to supply the needs of the foetus. However, there is evidence of a two-way transfer of thyroid hormone through the placenta: the myxoedematous mother of a normal baby loses her signs of myxoedema during pregnancy; these return after parturition, and an infant with no thyroid may be quite well developed at birth and show signs to suggest its deficiency only after several weeks. Signs may, however, be detectable quite early, and one mother of a second cretin recognized that her baby was not normal "from the first." Birth weight may be above the average, but this is by no means a constant finding.

It is often said that the condition cannot be recognized before 6–9 months, and Zondek (1944) states that there is no indication for treatment until the infant is between 1 and 2 years old. It is true that most cases come under

observation between 6 and 12 months, but several of my cases have been recognized before the age of 4 months, and one at 7 weeks (see Figs. 1 and 2) and one at 6 weeks. The importance of recognizing the condition during the time of most rapid growth of brain and body cannot be overemphasized.

The 6-weeks-old baby was referred because of "the sudden appearance of bilateral supraclavicular tumours"; axillary pads were also present. The 7-weeks-old baby came with a provisional diagnosis of "jaundice." In this infant the yellow colour, which is due to the carotenaemia resulting from lack of conversion of the carotene to vitamin A in the absence of thyroxine, was unusually deep, and certainly simulated jaundice. The conjunctivae were, however, unpigmented.

FIG. 1.—Case 4 at 7 weeks.

The commonest complaint before the age of 4 months is that the baby has become slow in feeding and is becoming more lethargic. In spite of the low intake of food, the weight increases for a time and the quiet fat baby may be accepted as a godsend. The yellowish pallor may suggest anaemia. Indeed, anaemia may be present, but it does not respond to iron. Umbilical hernia or abdominal distension and/or increasing constipation may bring the parents for advice. After the age of 4 months the heavy features, the usually dry, cool skin, the protruding tongue, the dull, sad expression, the hoarse voice, and the myxoedematous firmness of the tissues which gives a peculiar stiffness of the limbs, gradually appear, making the full picture of the 9–12-months-old toothless cretin. By then the retarded mental and physical development has become quite apparent. In one infant in our series the nature of the condition went unrecognized until the age of 2¼ years, by which time she was wasted, hypotonic, and almost immobile (Figs. 3 and 4).

FIG. 2.—Case 4 after treatment; aged 5 months.

Group II: Post-infective Hypothyroidism

In this group were six cases (four female and two male).

These are children in whom one can be reasonably sure that post-natal development has progressed normally for some time, normality being judged by the age at which the milestones of infancy have been passed and by the stage of ossification. Symptoms date, commonly though not quite invariably, from some acute infective illness such as whooping-cough or pneumonia. The interval between the acute illness and the parents becoming conscious of delay in further development is a matter of months, which varies to some extent according to the parents' acquaintance with normal children and to their powers of observation. The signs of hypothyroidism are not so striking as in the previous group, but evidence of delayed skeletal development may be seen in an open anterior fontanelle; the number of teeth is inadequate for the age, supraclavicular pads can usually be felt, and the child looks unnaturally solemn. He is short for his age, and the proportions tend to be of the infantile type; he is physically inactive and does not show the normal zest in his play. Usually he is mentally dull, but there may be no true mental impairment.

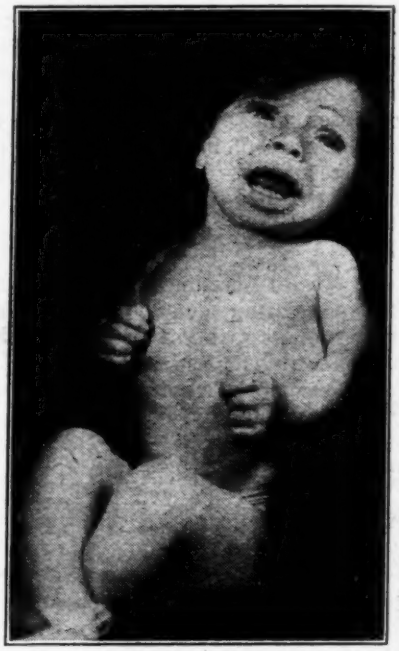

FIG. 3.—Case 12. Photograph taken on May 1, 1945, at 2¼ years. Before treatment.

These patients are usually referred to as cases of juvenile myxoedema, but the term "post-infective hypothyroidism" seems preferable. The gland may be damaged by infection at any time in post-natal life, and the term "juvenile" is not always applicable.

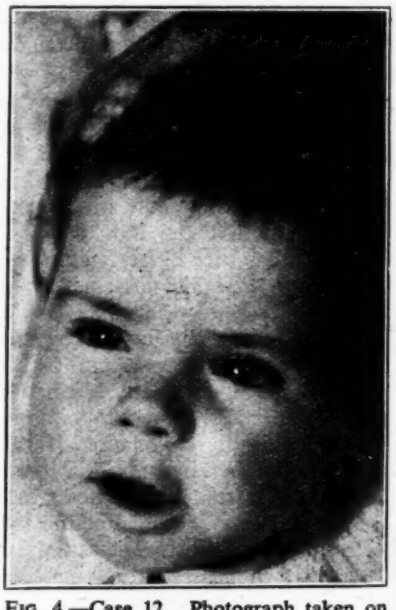

FIG. 4.—Case 12. Photograph taken on September 18, 1945.

Group III: Endemic Cretinism

In this group were nine cases—seven (four female and three male) from those successfully followed up, and two of the three adult women.

These cases differ in many respects from those already described. They came under observation late—only one before the age of 2 years. The history is vague and the mother is usually unable to say when she first became worried about her child's progress. The child has never been very active and has never displayed much interest in his surroundings; teeth have been cut late; he has learned to walk late, and to talk still later; the voice is gruff, not just hoarse, and the sounds produced may be quite inarticulate. Myxoedema is not pronounced in the majority, but there is always considerable stunting of growth. A goitre

was present in two patients when first seen; a third patient developed a goitre at 16 years. One patient was deaf. With one exception the mental level was low, and three (and probably a fourth, but he is still only 2 years old) would be classed as idiots. Two had spasticity of the limbs, and one of these had epileptic attacks. Two of the adult women were in this group, and one of them had a large nodular goitre. In childhood both were treated with thyroid extract for several years, but, according to the mother of each, "it did not make much difference." Both are very stunted and both have a very low intelligence (Fig. 5).

Dwarfism, goitre, and poor response to thyroid medication are accepted characteristics of endemic cretinism, and McCarrison (1917) also regards spasticity of the limbs and convulsions as features of that condition. Cases presenting such signs he calls "nervous cretinism," which he defines as "cretinous idiocy with associated diplegia and tetany due to fibrosis of the thyroid and parathyroid glands." He found that one-third of all Himalayan cretins were of this type. Thomson (1925) found three such cases among 62 cretins. In these cases brain damage is probably a part of the general degenerative state, and the spasticity and convulsions are due to that. But carpo-pedal spasms, which do occur, are more likely to be related to associated fibrosis of the parathyroids: Himsworth and Maizels (1940) report such a case. I contend that the cases in this group are relics of endemic cretinism and not examples of simple hypothyroidism.

FIG. 5.—Case IX aged 26 years. Dwarfed; goitre; imbecile; made no response to treatment in childhood.

The first group is the most important, for on early recognition and adequate treatment during the period of most active growth of the brain the child's future largely depends. Cases in the second group are perhaps more readily recognized, because arrest of development in a previously normal child attracts attention, and, even if the condition is not immediately diagnosed, delay in starting treatment is less serious than in the first group. The older the child when hypothyroidism develops, the truer this is. The third group is the least satisfactory from the point of view of success in treatment.

Clinical Features

The thyroid hormone seems to be responsible for the normal development of all tissues, but when it is deficient the various tissues are not affected equally, nor are the corresponding systems in different patients.

Skeletal System

The most constant changes are to be found in the skeletal system, in the arrest of growth. The infantile proportions persist so that the long body and short limbs may suggest a diagnosis of achondroplasia. The disturbance of growth of the bones of the skull, the endochondral bone being affected more than the membranous bone, is reflected in the naso-orbital configuration, which is responsible, in part at least, for the characteristic facies.

Radiographic examination of the skeleton provides an important diagnostic measure in revealing arrested growth, as shown in the increased density of the provisional zone of calcification and in the delay in appearance of ossification centres. The influence of thyroid therapy is shown in growth of bone within a few weeks, and the appearance of fresh centres of ossification within a few months. That the histological changes which normally take place in cartilage preliminary to calcification and ossification are disturbed is shown in the irregular calcification which proceeds under treatment. Instead of a single centre gradually spreading outwards to include the whole, multiple islets appear; these gradually coalesce and produce a fragmented appearance instead of one of uniform density. The longer the delay in beginning treatment the more apparent will be this sign, but only in those centres which should have shown ossification previously, while those centres which ossify at a later date do so quite normally. Wilkins and Fleischman (1941) regard this as "probably the most specific of all anatomic changes which are found in hypothyroidism" and give to it the name "epiphysial dysgenesis."

The changes subsequent to epiphysial dysgenesis tend to be most marked in the head of the femur, and are accompanied by changes in the femoral neck. It seems likely that, although the primary factor is a disturbance of maturation of the cartilage before ossification, mechanical strain is contributory. Deformity of the head and neck develop and are responsible for a waddling type of gait.

Muscular System

Atony of the muscles is a common, though not constant, feature of the untreated cretin. In the adequately treated cretin, also, in whom signs of hypothyroidism have disappeared, atony of the muscles may persist to such a degree that a diagnosis of familial muscular dystrophy may be suggested. The method of walking up steps and of rising from the recumbent position may closely resemble that seen in pseudohypertrophic muscular dystrophy.

Alimentary Tract

Bastenie (1946), in writing of paralytic ileus in the myxoedema of adults, states: "The possible importance and severity of the intestinal signs and symptoms in myxoedema do not appear to have been sufficiently emphasized." Symptoms related to the alimentary tract —lack of appetite, slowness in feeding, constipation, meteorism—though well known to be symptoms of the condition in infants, are easily misinterpreted when they are the presenting symptoms. In a child who is being treated inadequately, a chronic type of diarrhoea may develop, due presumably to the myxoedematous state of the mucosa, which will clear up only when the dose of thyroid extract is suitably increased. On the other hand, in spite of adequate therapy, constipation of the type associated with megacolon—abdominal distension, palpable faecal masses, and incontinence—may develop. In three children treated from infancy this occurred, and a dilated colon with a long sigmoid was demonstrated by barium enema at the ages of 3½, 6½, and 10 years. In such children the faecal incontinence might be attributed to subnormal mentality and appropriate treatment be withheld.

Blood

In the hypothyroidism of children, as of adults, some degree of anaemia is usually present. In general it is not severe and bears no relation to the severity of other signs

of hypothyroidism. Occasionally it is the presenting feature, in which case it may be mistaken for simple nutritional anaemia or, especially in infants, for haemolytic anaemia because the colour due to the lipochromaemia resembles that of bilirubinaemia.

In most of my cases anaemia has been slight and of the normocytic orthochromic type. With two exceptions, the haemoglobin has been above 60% and the red cells above 3.5 millions. I have no clear case of macrocytic anaemia, which is said to be the essential anaemia of hypothyroidism (Bomford, 1938), but in a few cases microcytosis has been recorded. The change which took place on treatment was very variable. In one child aged 5 months, in whom general signs were minimal and who presented as a case of anaemia, the haemoglobin rose from 50% to 65% in a month on treatment with thyroid extract only. Another of the same age, who presented the classical picture of cretinism, had a haemoglobin of 70%, which remained at this level during four months' treatment with thyroid. When microcytosis was present it was necessary to give iron as well as thyroid extract—that is, an iron-deficiency anaemia was superadded to the essential anaemia of thyroid deficiency.

It is interesting to note that a fall in haemoglobin and red cells sometimes occurs during the early weeks of treatment, a point observed originally by Vaquez in 1897. This is due to restoration of the plasma volume. The reticulocyte response to thyroid administration is, of course, a useful point in diagnosis.

The exact pathogenesis of anaemia in thyroid deficiency is a problem which is still unsolved.

Biochemical Findings

Cholesterol.—There seems to be a close relation between basal metabolic rate and blood cholesterol, but whether thyroxine has a specific effect on cholesterol metabolism (Hoffmann and Hoffmann, 1944) or merely influences the shift of the cholesterol to and from the blood plasma (Fleischman and Shumaker, 1942) is undecided. In normal children the blood cholesterol has a wide range, but, excluding cases of nephrosis, a level of above 200 mg. per 100 ml. may be regarded as confirmatory evidence of hypothyroidism; however, the cholesterol level may be well within normal limits. In the cases under review the initial level ranged from 116 mg. per 100 ml. in a 5-months-old baby to 479 mg. in a 4-year-old girl. The effect of thyroxine is perhaps of more value in diagnosis; in a normal child the cholesterol will fall after a single dose of thyroxine but will return to normal quickly, while in the hypothyroidic child the fall will last for several weeks (Wilkins and Fleischman, 1941). The blood cholesterol level is of value in judging adequacy of treatment, and in this respect is certainly a more sensitive test than *x*-ray examination of the bones, though perhaps less sensitive than the electrocardiogram.

Phosphatase.—A low serum phosphatase level is common but not a constant feature, and it rises on administration of thyroid.

Calcium and Phosphorus.—Aub and his collaborators (1927) found that in hypothyroidism there is a diminished rate of exchange of calcium and phosphorus, these substances being deposited in greater concentration in the bones and eliminated less freely in the urine and the stools than they are in the normal. Their actual concentration in the blood is not greatly altered. This observation was confirmed by Robertson (1941), who studied the calcium and phosphorus metabolism in three cases of myxoedema in adults. He found that the blood serum level of calcium and phosphorus was normal but the output greatly reduced, and that the reduction was greater in the urinary calcium than in the faecal calcium. After thyroid therapy the output of both calcium and phosphorus rose, the increase being mainly in the urine. I have found no similar studies in children, and our attempts to investigate calcium and phosphorus balance were unfortunately unsuccessful. There was, however, clinical evidence of calcium retention, increased density of the bones being present, and one patient (Case 12) had a diffuse calcinosis of the soft tissues (Fig. 6).

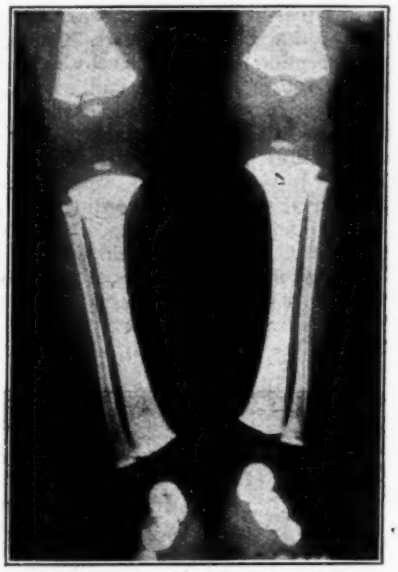

FIG. 6.—Case 12. Radiograph showing diffuse calcinosis, untreated before age 2¼ years.

The patient, a girl aged 2¼ years when first seen, was a very extreme example of untreated congenital hypothyroidism. The powdery appearance of the soft tissues was revealed on routine *x*-ray examination of the long bones. Under treatment, the calcinosis appeared to increase at first (presumably it became more apparent because of loss of tissue fluid), and then gradually cleared. The effect of thyroid on the blood chemistry is shown in Table I.

TABLE I.—*Effect of Thyroid on Blood Chemistry in Case 12 (Group I)*

Date	Calcium (mg. per 100 ml.)	Phosphorus (mg. per 100 ml.)	Phosphatase (Units)	Cholesterol (mg. per 100 ml.)
30/4/45	10·9	7·2	4·9	371
2/5/45 (Thyroid therapy begun)				
5/6/45	11·3	5·3	8·8	244
17/7/45	12·5	5·3	11·8	225
19/9/45	11·7	7·3	13·0	—
15/10/45	11·5	4·9	15·7	113
21/5/46 (Thyroid increased)	11·7	6·2	8·0	123
6/2/48	10·0	4·3	12·5	181

When seen in May, 1946, cretinoid features were obvious; until then the infant had been having 1 gr. (65 mg.) of thyroid extract daily; this was increased to 1½ gr. (0·1 g.) and later to 2 gr. (0·13 g.) daily with corresponding physical improvement and improvement in blood chemistry.

Heart

The alteration in the size of the heart, with and without treatment, which occurs in adults is rarely seen in children, and bradycardia is not a feature. But sometimes an extreme cyanosis of the extremities bears witness to the indolent action of the heart, and the electrocardiogram usually shows a quite characteristic change from the normal.

The characteristic signs are a low-voltage curve, with flat P and T waves; the P–R interval is usually normal, but occasionally it is lengthened; and more rarely the Q–T interval is lengthened. Various explanations have been offered for these electrocardiographic findings, but it seems likely that they are due mainly to the myxoedematous changes in the myocardium and to changes in the conductive mechanism. A typical tracing is shown from Case 12 before treatment, and the return to normal after six months' treatment (Fig. 7).

The E.C.G. is also perhaps the most sensitive test of adequacy of treatment. In diagnosis, electrocardiography is probably of no greater value than the more commonly used *x*-ray examination of the bones.

Treatment and its Control

Children, and especially infants, suffering from a deficiency of thyroid hormone are particularly sensitive to its administration, and it is important that the initial

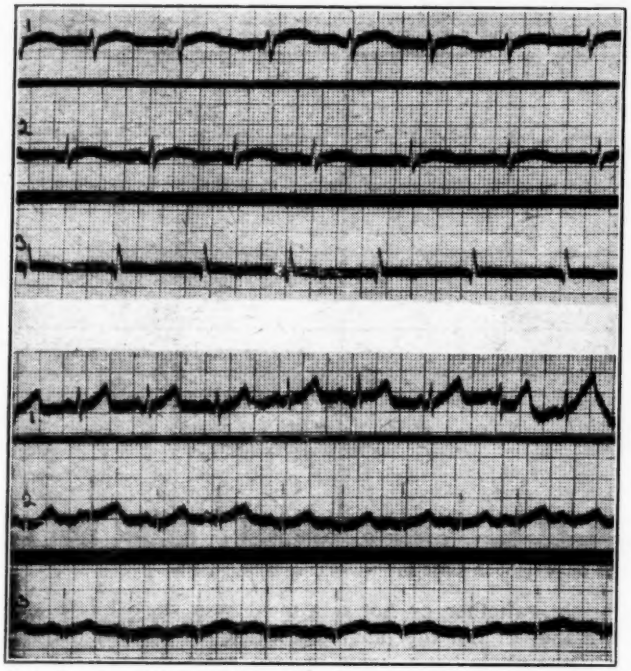

FIG. 7.—Case 12. E.C.G. on April 30, 1945, before treatment, and on October 3, 1945, after six months' treatment.

dose should be low. The characteristic swelling of subcutaneous tissue, presenting as a generalized non-pitting oedema and localized as supraclavicular and, more rarely, axillary pads, is due to an extracellular accumulation of mucoprotein which exerts sufficient osmotic pressure to withdraw fluid from the plasma to the extracellular spaces. The first effect of thyroid treatment is to dissipate the mucoprotein, and the associated fluid is excreted. This is seen in the rapid disappearance of the supraclavicular pads within a week or so of the start of treatment, and in a loss of weight due to fluid loss. If dosage is incautious the loss of both extracellular and intracellular fluid may be so great that the infant becomes dehydrated to a dangerous degree. A daily dose of ⅛ gr. (8 mg.) of the extract, or ¼ gr. (16 mg.) on alternate days, is safe, and it should be increased by that amount at intervals of four to five days. As a result of therapy the infant begins to feed more willingly, the subnormal temperature becomes normal, the colour improves, and the facial expression changes.

Signs of too high dosage are a sudden rise in temperature occasionally, an increased frequency of stools, and further loss of weight. If such signs occur thyroid should be stopped for two to three days and then restarted at a slightly lower level. The dose thus reached can then be given for several weeks or even months, so long as its adequacy is checked by improvement in the level of the blood cholesterol and by evidence of satisfactory growth of bone; the latter can be observed within a few weeks, although fresh ossification centres may not appear for about three months. As a safeguard against overdosage, it is a good plan to omit the dose on one day in each week; in some cases it can be omitted on two days a week. Irritability in the early weeks of treatment is not, of itself, an indication for reduction of dose, but should be countered by giving a sedative such as phenobarbitone.

For at least three months the child should be under close supervision, and thereafter his general condition should be reviewed and an estimate made of the need for any alteration in dose at intervals of 3, 6, and, later, 12 months, until the stage of puberty has been passed. The immediate improvement in physical appearance is so dramatic that both parents and doctor are apt to be too easily satisfied. It is important to realize that, while the maintenance dose required varies greatly in different patients, the length of time for which it remains adequate also varies. The most common mistake lies in a failure to increase the dose periodically, and underdosage is now of much greater danger to the patient's ultimate well-being than overdosage. Another point of importance is that progress is not always "even," and a balance must be struck between the effect produced on body growth and that on the nervous system: a child with a satisfactory I.Q. may have a bone age below her chronological age yet an increase in dose might only lead to irritability.

The dangers of a too high initial dose and of a failure to increase the maintenance dose are shown in the following case.

Case 6.—A boy born in January, 1942, with a birth weight of 8 lb. 5 oz. (3.77 kg.), was seen at the age of 3 months, when he had the general appearance of a cretin. His temperature was between 95 and 96° F. (35 and 35.6° C.) and the pulse rate 130. He was given thyroid extract, ½ gr. (32 mg.) daily, and a state of dehydration supervened, necessitating the administration of parenteral fluid. The weight continued to fall for two days after stopping thyroid and then began to rise (Fig. 8). Thyroid extract was restarted, ¼ gr. (16 mg.) daily, then alternated with ½ gr., and all seemed well. When ½ gr. was given daily the weight again fell. Ultimately a satisfactory dose of ½ gr. on five days a week was reached. By the age of 18 months he was trying to walk and his bone age was up to normal. I did not see him again until he was 7 years and 10 months, when, in October, 1949, he was sent back because of a chronic diarrhoea of 12 months' duration. The dose of thyroid had never been altered from that of ½ gr. five days a week. He now presented the general picture of hypothyroidism, with a yellowish colour, cretinoid features, and a somewhat fatuous expression. His height was 43½ in. (110 cm.), and his bone age that of 3 years. The E.C.G. showed evidence of hypothyroidism; the blood cholesterol was 267 mg. per 100 ml. Thyroid extract was increased to 1 gr. (65 mg.), and later 2 gr. (130 mg.) daily. The blood cholesterol fell to 188 mg. within three weeks; the E.C.G. showed improvement within 18 days; the diarrhoea ceased. In six months he grew 2½ in. (5.7 cm.).

In treating older patients the scheme followed is of course similar, but the initial dose need not be less than ½ gr. daily, as after infancy the danger of initial overdosage is very much less. There is an important exception, however, in the type of child who would most likely belong to Group II. Where the mental level is relatively high, thyroid extract may produce a manic type of psychosis unless the initial dose is low and is increased very gradually. Means (1948) describes such a case.

A child under treatment may appear to be so normal that doubt is raised whether continued therapy is necessary, and a failure to recognize that the appearance of normality is in fact due to the therapy too often leads to thyroid extract being withheld. If there is any reasonable doubt it is certainly right to withhold thyroid, but this should be done only under controlled conditions. The general effects of withdrawal may become apparent quickly, but they may appear very insidiously and several weeks may elapse before hypothyroidism is again apparent, by which time the patient may be lost sight of. The effects of withdrawal can and should be observed by regular weekly, or at most fortnightly, examinations

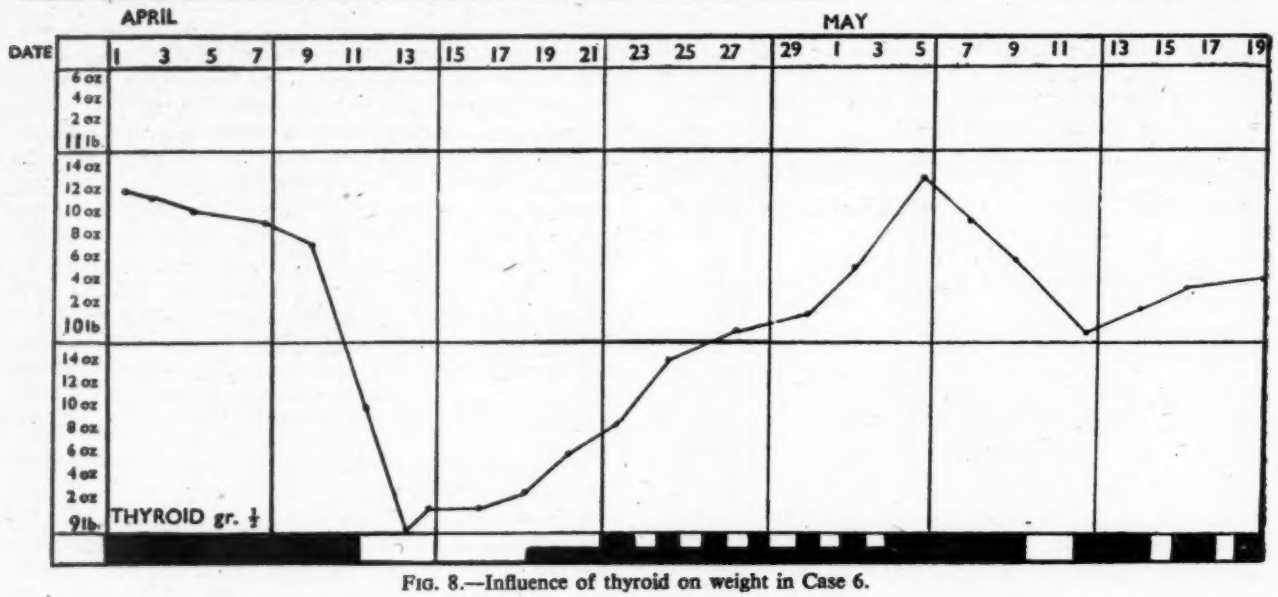

FIG. 8.—Influence of thyroid on weight in Case 6.

of blood cholesterol or by the electrocardiogram. Here the E.C.G. is the most sensitive test.

Although continued overdosage is much less common than underdosage, it does sometimes occur and is revealed by a failure to gain weight and by undue excitability. The child is aimlessly restless and the powers of concentration so impaired that he is unable to learn and is apt to be credited with less intelligence than he has. Bruch and McCune (1944) lay emphasis on this point, and I am sure it is important.

In cases in which treatment has been started late or in which there is an underlying cerebral defect or in cases of Group III, it may be necessary to allow physical signs of hypothyroidism to persist rather than change a placid defective child into an unmanageable one. That is a matter of common sense. It is certainly wrong to push thyroid in the hope of raising the mental level if all physical signs have disappeared.

In the early days of treatment especially, as growth is then more rapid than normal, adequate vitamins should be given, for it is easy to allow rickets to develop.

Results and Prognosis

There is no difficulty in foretelling the immediate effects of thyroid therapy, but it is wellnigh impossible to make an ultimate prognosis with certainty, though it is right and justifiable to give a hopeful one.

Skeletal growth is stimulated. In older, previously untreated, hypothyroidic children during the first year of treatment the rate of growth may be 600% of that of the year preceding treatment, and 200% over the normal for the age, while in the second year the curve falls to 25% of the previous annual increment and in the third year the child will grow at approximately normal rate (Shelton, 1942). According to Shelton, the ability to grow and to differentiate much more rapidly than normal, as a result of treatment, seems to increase with the years up to somewhere between 10 and 15 and then gradually decreases. This remarkable fact was reported by John Thomson (1896) at the Annual Meeting of the British Medical Association in 1896, when there took place what was probably the first discussion on the influence of thyroid in the treatment of cretins.

The increased rate of growth is seen in cases in Groups I and II; these children became normal in height, whether or not treatment was started late and whether or not the intelligence reached a normal level. On the other hand, cases in Group III did not show a rapid initial growth but progressed at a slow steady rate and remained well below the average, except in Case I, who was also the only one in this group whose intelligence was above 70%.

Teeth erupt fairly rapidly after treatment is begun, but the primary dentition may not be complete until the age of 2½–3 years. Permanent teeth tend to appear early. Dental caries develops early; it is severe, and affects permanent as well as temporary teeth. It is most severe when treatment has been most delayed.

Menstruation, though somewhat late in onset, is usually quite normal. This is probably quite independent of treatment, for even untreated cretins may become sexually mature and capable of reproduction.

The real difficulty arises in attempting to foresee what will be the mental development in any particular case. Gesell *et al.* (1936) think that there may be two types of cretin, one in which both mental and physical retardation are due to hypothyroidism, and one in which the essential condition is primary amentia with superadded hypothyroidism. They consider that "immediacy of response" [to thyroid] "is an important prognostic indicator," and state that the entire gain in development quotient is accomplished in the first two years of treatment—years accordingly of critical importance. Goodkind and Higgins (1941) studied 23 patients who had been under treatment for 5½ to 24 years. Usually the dwarfed patients had a lower I.Q. than those of normal growth, and the age of diagnosis and the beginning of treatment were usually earlier in the ultimately mentally retarded cases than in those of normal intelligence. They considered that, as the ultimate mental capacity of the hypothyroid child under adequate treatment was not strictly related to physical growth, to delay in beginning treatment, or to the dose of thyroid necessary for normal metabolism, the cerebral deficiency could probably be regarded as congenital and from the same cause as the thyroid damage. Bruch and McCune (1944) review the literature, and from their own study of 23 cases conclude that mental capacity shows "noteworthy independence of the amount of treatment." They consider that "the functional development before treatment supplies an index of the capacity for future mental development."

Aubrey Lewis (1937) surveys 79 patients who had been treated with varying degrees of adequacy. He concluded that, although there is a rough correspondence between results and promptness and continuity of treatment, these alone are not decisive factors; the stage of development before the onset of symptoms, the inherited intellectual capacity, and the general environment are also important.

Radwin and his colleagues (1949) think that the outlook in congenital hypothyroidism is not so bleak as has hitherto been pictured. They studied 12 cases and compared early with later psychometric tests, finding that in the majority the I.Q. had risen. Nine of their patients became normally functioning self-supporting people, and three were mentally retarded. Thompson (1941) considers that absence of thyroid function for only a few months results in some permanent damage to the rapidly growing brain of the infant and that in most cases some irreparable damage has been done before the diagnosis is made.

My findings are in agreement on some of these points but not on all. The possible mental development of any child depends primarily on its inherited intellectual capacity, and that, broadly speaking, depends on the intellectual level of its parents. This is doubly important in the case of the cretin, for, excepting the few cases in which there is an underlying cerebral defect, the more intelligent the parents the greater the potential of the child, the more likely is it that the child's abnormality will be recognized early, and the more likely is it that the need for regular and continuous treatment will be appreciated. Intelligent parents are more able to handle the child with patience and encouragement during the early years of its slowly developing faculties. McDonald, Brown, and Bronstein (1940) stress the importance of the parental attitude in its contribution to the child's ultimate intellectual and social development.

The immediate improvement in appearance in response to treatment, the increase in emotional response, and the change of a sad-looking immobile child into a smiling active one may raise hopes unduly. Then follows despondency, for further development seems to proceed more slowly. There is slowness in learning to walk: children who come under treatment reasonably early may walk between 1½ and 2 years, and, in some, delay is due in part at least to muscular hypotonia. Schreiber and his colleagues (1940) made an intensive study of the speech of thyroid-deficient children. They found that the children were able to express most elemental sounds and that there was some relation between age and intelligence and the various errors of speech. They state that "some cretins developed language facilities within the short space of six weeks" and suggest that with thyroid medication there was a "sudden release of the speech mechanism." I certainly saw a sudden release of the walking mechanism in one case, but have not seen anything similar in relation to speech. It is difficult to know, from parents' statements, at what age a child begins to talk, but it can be observed that the hoarse voice soon becomes soft; progress from sounds to syllables, and from syllables to words and sentences, is at a slower rate than with normal children. The great majority ultimately learn to talk quite distinctly, but in some a slowness in speech persists and the words tend to be slurred. In a few there is a definite speech defect. The possibility of a defect in hearing should be kept in mind, but the incidence of deafness is low except in endemic cretinism.

This slowness in learning new things remains, and is noted in school reports along with the almost constant remark that "arithmetic is poor." A child who is slow is not necessarily stupid, and a wrong estimate may easily be made. This fact indicates the need for more individual teaching of these children. Many of them are reported to have good memory, and to have good powers of concentration and of perseverance.

Much helpful information can be obtained by regular use of intelligence tests, and I am greatly indebted to Dr. Joan Greener, who has kindly examined my patients and has assessed their I.Q.s, using the Stanford revision of the Binet–Simon tests (see Tables II, III, and IV).

TABLE II.—*Group I*

Case	Sex	Age When First Seen	Previous Treatment	Present Age	Skeletal Age	I.Q.	Treatment
1	F	6 weeks	None	5 years	4 years	102	Continuous adequate
2	F	3 months	,,	14 ,,	N	86	,, ,,
3	F	15 ,,	,,	18 ,,	N	85	,, ,,
4	M	7 weeks	,,	5½ ,,	N	80·6	,, ,,
5	M	3 years	Inadequate from 1 year	10 ,,	N	80·6	,, ,, from age 3 years
6	M	3 months	None	8 ,,	At 1½ yrs=1½ yrs At 7½ yrs=3 yrs	80	Inadequate between 1½ and 7½ years
7	F	13 ,,	,,	7½ ,,	N	79·2	Continuous adequate
8	M	23 ,,	,,	4½ ,,	N	71	,, ,,
9	F	4 years	Inadequate from 10 months	7½ ,,	At 4 yrs=2 yrs At 7½ yrs=N	65	Adequate from 4 years
10	F	9 months	None	8 yrs 10 mths	N	51	Continuous and adequate (probably primary mental defect)
11	M	3½ ,,	,,	8½ years	N	42·7	Discontinued for 4 months in first year. Always irregular
12	F	2½ years	,,	7 ,,	N	34	Adequate but very late in being started
13	F	10 months	For 2 months	4½ ,,	2 years	<50	Inadequate

TABLE III.—*Group II*

Case	Sex	Age When First Seen	Previous Treatment	Present		Probable Cause	Treatment
				Age	I.Q.		
A	M	4 years	None	6½ yrs	128%	Febrile illness at 1 year 9 months	Adequate
B	M	5½ ,,	,,	12 ,,	110	Symptoms date from age of 3 years	,,
C	F	4 months	,,	4½ ,,	90	Simple pemphigus at 10 days	,,
D	F	20 ,,	,,	4½ ,,	73·7	Pneumonia at 9 months	,,
E	F	22 ,,	,,	4½ ,,	70	Whooping-cough at 9 months	,,
F	F	5 years	,,	10 ,,	52·8	,, ,, 11 ,,	,,

TABLE IV.—*Group III*

Case	Sex	Age When First Seen	Treatment Started	Present Age	I.Q.	Remarks	Height
I	M	10½ years	10½ years	12 years	90·4%	Has a goitre; mother and her two sisters and father are deaf	Low average
II	F	4½ ,,	4½ ,,	18 ,,	65%	Deaf; goitre from age 15–16 years. Earns £2 10s. weekly	Below ,,
III	F	7 ,,	7 ,,	11½ ,,	<70%	Attends special school	,,
IV	F	5 ,,	5 ,,	—	<50%		Dwarfed"
V	M	2½ ,,	2½ ,,	10 years	<30%	Spasticity of lower limbs	
VI	F	10 ,,	2 ,,	10 ,,	<30%	Spasticity of lower limbs; has fits	
VII	M	1½ ,,	1½ ,,	22 months	<50%	Has goitre	
VIII*	F	38 ,,	Early childhood	38 years	<30%		Dwarfed
IX*	F	26 ,,	4 years	26 ,,	<30%	Developed goitre in early 'teens	,,

Except in first two, I.Q. is a personal estimate. * Seen once only.

Conclusions

Cases of hypothyroidism as we see them in the Midlands can be placed in three groups. In attempting to give a prognosis this classification is helpful, for prognosis depends primarily on the particular type of case.

In those cases which bear some resemblance to endemic cretinism (Group III) there is a constitutional degenerative state (Zondek) associated with hypothyroidism. They can be recognized by the history of slow mental and physical development before definite signs of thyroid deficiency supervene; goitre may be present early or may develop during adolescence. In these, prognosis is not good; they are likely to remain undersized and the intelligence is likely to keep at a low level; epilepsy may supervene and the limbs may be so spastic that walking is impossible. This is a group that is probably dying out.

In contrast, in those cases in which there is a period of normal development and signs of hypothyroidism appear after some acute infective illness (Group II), the outlook is good and normal physical and mental development may be expected. The later the onset of symptoms the better the outlook, and the length of the interval between the onset of symptoms and the start of treatment seems to be of less importance than in the cases of Group I.

In congenital hypothyroidism (Group I), which is easily the largest group, signs appear in infancy. Here prognosis seems to be intimately related to early diagnosis and to early and adequate treatment. I do not agree that the earlier the appearance of symptoms the worse the prognosis, but the earlier their appearance the more important it is that diagnosis should be made early. In this group growth will be normal. In a small proportion of cases there may be an underlying cerebral defect which is revealed by thyroid medication, but the epigrammatic statement "that you treat the cretin and unmask the idiot" is far from being universally true. Treatment requires detailed supervision over many years. With early diagnosis and careful treatment, most of these children can be brought to a level which makes it possible for them to be admitted to an elementary school —a point of great practical importance. Some find their way into the "average" stream, and now and then into the upper regions of average. Some would be helped greatly by individual teaching in the early school years. Even when scholastic attainment is not high, they become pleasant members of the family and self-supporting members of the community.

I am indebted to Professor K. D. Wilkinson and Dr. Clifford Parsons for the electrocardiogram, and to the hospital photographer, Mr. A. G. Williamson, and his assistant, Miss B. Field, for the photographs.

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Western Europe, which has been dependent on Marshall Plan aid for life-saving drugs, is beginning to produce its own penicillin, streptomycin, and other antibiotics, according to a report from the Economic Co-operation Administration. Production is, however, still far from being self-sufficient. E.C.A. has so far financed about $50,000,000 worth of drugs, mostly penicillin and streptomycin, for countries faced with high mortality rates from tuberculosis and other diseases following the war. American equipment for the construction of plants in France (at Vitry-sur-Seine and La Plaine St. Denis) has been provided by the organization, and France is manufacturing other antibiotics and has enough penicillin for export. Italy now has a penicillin plant which is supplying 40% of the country's needs. New equipment is being installed which is designed to increase the output to 60% of the required amount by the end of the year. Additional production capacity that has been planned will put Italy well on the way to being self-sufficient in all forms of penicillin and the same will apply to streptomycin when the Laboratoria Plama in Rome reaches full production level in September. Other countries, such as Belgium, Luxembourg, and Denmark, are also making considerable progress in the production of drugs, but Greece is still dependent upon imports of penicillin and streptomycin, although she produces some sulpha drugs.

EXPERIMENTAL STUDY OF 79 CASES SHOWING THE EARLY POST-GASTRECTOMY SYNDROME

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At the present time partial gastrectomy seems to be the standard procedure when peptic ulcer presents a surgical problem. All authorities are agreed on the satisfactory nature of results, but the unpleasant symptoms, termed the "post-gastrectomy syndrome," which sometimes occur after operation continue to attract considerable attention. Indeed, the symptoms may be so severe and disabling as to make the patient a "gastric cripple" (Custer, Butt, and Waugh, 1946).

Perusal of the existing literature reveals the following hypotheses which have been offered to explain the causation of the syndrome: (1) Rapid emptying of a small gastric remnant, with jejunal filling and distension, due to absence of a sphincteric mechanism between the stomach and small bowel (Hurst 1913; Mix, 1922; Reingold, Schwartz, and Necheles, 1942; Custer, Butt, and Waugh, 1946; Adlersberg and Hammerschlag, 1947, 1949; Irvine, 1948). (2) Delayed emptying of the stomach remnant (Snell, 1937). (3) Reflux of food into the afferent loop of the anastomosis and into the duodenum (Finsterer and Cunha, 1931; Ogilvie, 1935; Lake, 1937; Maingot, 1940; Marshall, 1944; Ingelfinger, 1944; Wangensteen, 1945; Monro, 1945; Mimpriss and Birt, 1948). (4) Coincident hyperglycaemia due to rapid absorption of carbohydrate (Glaessner, 1940). (5) Reactive hypoglycaemia subsequent to the initial hyperglycaemia (Lawrence, 1936; Evensen, 1942; Gilbert and Dunlop, 1947; Barnes, 1947; Adlersberg and Hammerschlag, 1947, 1949; Zollinger and Hoerr, 1947). (6) Coincident gastrojejunitis (Porges, 1947). (7) Absorption of fluid into the jejunum as a result of too rapid entry of hypertonic solutions (Machella, 1949).

Much confusion has been caused by failure to establish exact time relationships between the occurrence of the symptoms and the various features observed as possible causes. In the attempt to elicit the aetiological factors of the post-gastrectomy syndrome, the most valuable concept is that offered by Adlersberg and Hammerschlag (1947), and confirmed by Zollinger and Hoerr (1947) and Avery Jones (1948, personal communication). These authorities believe that there are two distinct syndromes—an early type coming on at the end of a meal, or within a few minutes of its completion, and a late variety, occurring during the second or third hour after a meal.

This paper presents the results of a study of the post-gastrectomy syndrome over the past three and a half years. From 660 cases of patients who had survived partial gastrectomy performed for benign peptic ulcer and who had been carefully sifted, 79 cases showing the early post-gastrectomy syndrome were collected. It is not without significance that although 102 of the 660 cases reviewed were of the Billroth I type gastrectomy, all these 79 cases were of the Polya type. Up to the present time we have not seen a case of the early syndrome following the Billroth I operation. For the purposes of control, every fifth case without symptoms was also studied, thus affording 174 cases in all—79 with the syndrome and 95 controls. We have come to use the term "early syndrome" only with reference to those symptoms which occur during the first half-hour after a meal. The various symptoms so occurring and their relative frequency are shown in Table I.

TABLE I.—*Analysis of Symptoms in 79 Cases*

Epigastric fullness and distress	79
Pallor	76
Sensation of warmth	72
Nausea	64
Palpitations	50
Vomiting of bile-stained fluid	41
Eructations	9
Borborygmi	8
Vomiting of food	5
Sensation of cold	3

The precise aim of the present study has been to reproduce these symptoms by experimental methods in order to identify the cause.

A. Experimental Distension of the Jejunum with a Balloon

In this particular test the patient swallowed a Miller–Abbott tube and bag until about 18 in. (45 cm.) of it was in the gastric remnant as confirmed by *x*-ray examination. To get the balloon through the stoma into the jejunum was a most difficult task, and the simplest technique was found to be the best. The patient swallowed the tube on the day before the tests were performed. During the rest of the day he or she was encouraged to take all meals, to drink freely, and to walk around as much as possible. On the following morning the patient was screened to locate the balloon. A mouthful of barium emulsion was given to be swallowed, and this showed if the tube had passed through the stoma. When the attempt to pass the stoma was successful the balloon was usually situated about 12 in. (30 cm.) beyond the anastomosis in the efferent loop of jejunum.

In the 61 patients with the early syndrome who were subjected to this test the balloon passed into the jejunum 26 times, while in the control group success was obtained in 23 out of 53 attempts.

The effects of jejunal distension were tried in the morning before any food had been consumed. Initially, all the air in the balloon was aspirated, and then 80 ml., 100 ml., and 120 ml. of water was injected in turn, aspirating fully after each occasion and waiting half an hour or so between each injection to allow the effects of the previous distension to subside. The experiments were carried out first with the patient supine, then in the erect position. The results of these distension tests are shown in Table II, the figure in each case representing the number of patients in whom distension produced symptoms.

TABLE II.—*Effects of Jejunal Distension*

		Amount of Water in Balloon		
		80 ml.	100 ml.	120 ml.
Supine position:				
Cases with syndrome	26	5	19	26
Cases without syndrome	23	6	17	23
Erect position:				
Cases with syndrome	26	5	20	26
Cases without syndrome	23	5	18	23

The symptoms produced by this distension of the jejunum consisted of a vague sensation of fullness, on three occasions described as pain, and in every case the sensation was referred to the umbilical area. Three of the cases with the syndrome and two of the controls vomited bile during the performance of the tests in the supine position. In two cases only—one exhibiting the early syndrome and one of the controls—did the distension produce vasomotor effects—that is, tachycardia, pallor, perspiration—together with a sensation of nausea as well as fullness. The table indicates that posture does not affect the tests, the results of distension being almost the same in both the erect and the supine position. In addition, it seems that there is no difference in the sensitivity of the jejunum to distension, as both groups of patients appear to respond to an equal degree.

The effect of sympathetic splanchnic block was tried in some of these cases—in 20 with the syndrome and in 16 of the controls. With Kappis's technique 20 ml. of 1:2,000 solution of amethocaine was injected on each side of the first lumbar vertebra. The sensation produced by the balloon distension was abolished in 17 (85%) of the cases with the syndrome and in 11 (69%) of the cases of the control group.

Devine, of Australia (quoted by Aldersberg and Hammerschlag, 1947), stated that jejunal distension with a balloon in these cases produces no symptoms, while Machella (1949) believes that distension can produce them. The effect of balloon distension of the small bowel in normal individuals, however, has been observed repeatedly (Hurst, 1913 ; Barclay, 1936 ; Samson Wright, 1945). All these authors were especially concerned with the location of the sensations produced rather than their nature. In each case the raised tension within the jejunum caused by the distended balloon produced a sensation of fullness which was referred to the umbilicus.

As a result of these investigations, the following conclusions may be drawn: (1) jejunal distension produces a sensation of fullness referred to the umbilicus ; (2) jejunal distension does not usually produce any other symptoms ; (3) posture has no effect on the results of jejunal distension ; (4) there is no difference in the sensitivity of the jejunum between cases with the early postcibal syndrome and those without it ; and (5) sympathetic block (splanchnic) relieves the symptoms produced by jejunal distension.

B. Radiological Study

The aim of this study was to compare cases with and without symptoms in both the supine and the erect positions. In addition, since the early syndrome did not occur in 102 of the Billroth I cases reviewed, a series of these was studied also. The groups of cases were made up as follows: 72 Billroth I cases, 95 Polya cases without syndrome, and 61 Polya cases with syndrome. The number of cases with the syndrome was originally 79, but 18 of these did not attend for further observation.

In order to compare the findings in the supine and erect positions, screening was carried out in both, the stoma being occluded when the patient changed his position. In some cases the stomach was empty before the position could be changed. In the Billroth I series the position of the stoma was sometimes so high that occlusion was impossible. It was found that comparison of the state in the erect and supine positions was best achieved by a separate skiagram in each position showing all the vertebrae, the picture in each case being taken in the same phase of respiration.

The findings of this radiological study were as follows:

Billroth I Series (72).—Emptying of the stomach was complete within one hour in 65 of these cases (90%). In the remainder the stomach was empty in one and a half hours. Emptying was just as rapid in the supine position as in the erect. On occluding the stoma 17 (24%) of the series of 72 experienced a feeling of distension, but none had any vasomotor symptoms. The average width of the stoma appeared to be between 1.5 and 2 cm. In the change from the supine to the erect position the stoma descended, on the average, about 2 cm.

Polya Series without Symptoms (95).—The stomach was empty within 40 minutes in 91 cases (96%), whilst in the remainder a variable time between one and a half and two hours expired before emptying was complete. Afferent-loop reflux was seen in 21 cases (22%) in the erect position and in 25 cases in the supine position. The size of the stoma varied, of course, depending on the type of operation, and it ranged from 2 cm. to 8 cm. Occlusion of the stoma was difficult in these cases, but accumulation of barium in the stomach caused a feeling of distension in approximately one-third of the patients. Change from the supine to the erect position was associated with descent of the stoma, the average descent being about 2 cm. Although sometimes there was no descent apparent, on other occasions it was nearly 5 cm.

Polya Series with the Early Syndrome (61).—The emptying time in this series was 40 minutes for 57 (93%) of the cases. Afferent-loop filling was seen in 9 cases (15%). Again, as in group B, the size of the stoma showed variations according to the type of operation, but cases were equally scattered through the range. In this series 48 (79%) of the cases had symptoms during the examination. In all of them the symptoms occurred in the erect position, and in 17 (28%) it was observed that symptoms occurred while the barium emulsion was still in the stomach. The patients complained of fullness in the epigastrium, their pulse rate increased, they perspired, and two of them fainted. During screening, of course, pallor could not be seen, though it was obviously present when seen afterwards. In changing from the supine to the erect position the stoma was observed to descend on an average about 7 cm., the maximum being nearly 11 cm.

It was very difficult to evaluate this finding of descent, the degree of which appears to be greater in cases with the early syndrome than in cases without symptoms. In normal people there is considerable descent of the stomach in the change from the supine to the erect position. Thus, Moody and Van Nuys (quoted by Grant, 1946) have shown that the normal pylorus moves about 6–8 cm. with this change of position, whilst the lowest margin of the greater curvature moves a distance equivalent to the width of two vertebrae. The higher one ascends in the stomach the less is the range of movement. Moody and Van Nuys state that the most fixed position is the gastro-oesophageal junction. If this is so, the descent recorded may be interpreted as stretching of the gastric remnant. We were very careful to ensure that pictures were taken at exactly the same phase of respiration, so that the position of the diaphragm was constant. In this way descent relative to the diaphragm was measured. Figs. 1 and 2 show the descent in two cases with rapidly emptying stomachs. Although rotation of the gastric remnant around an axis through the gastro-oesophageal junction (the stoma moving downwards and to the left) would also account for apparent descent, this feature was not apparent in the radiographs. In any case, this rotation would be common to all cases except the Billroth I patients.

An observation common to about 70% of all the cases was as follows: The initial mouthful of barium, when

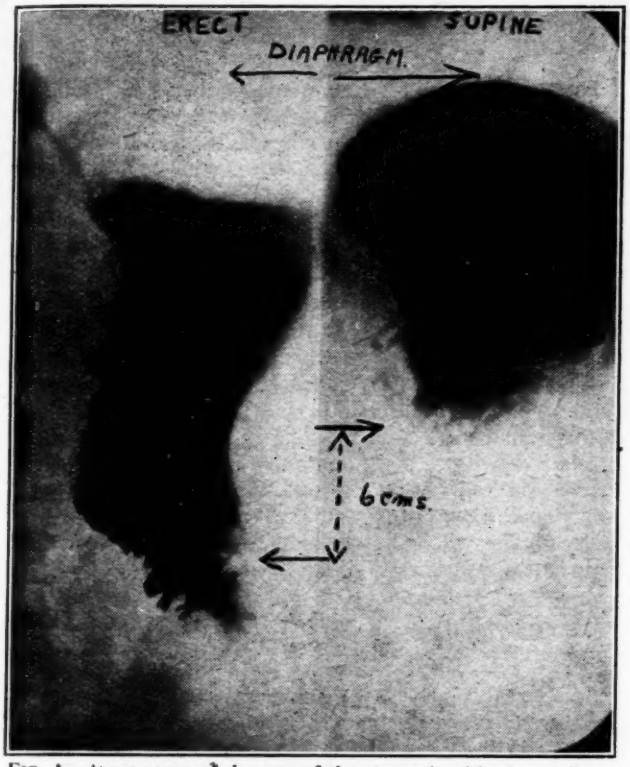

FIG. 1.—Illustration of descent of the stomach with change from the supine to the erect position (descent = 6 cm.)

swallowed, passed straight through the stomach into the jejunum. As more barium was swallowed egress from the stomach was definitely much slower, as though a primitive stretch reflex came into action, emptying being controlled by rhythmical contractions of the jejunal musculature.

Comment.—The findings of this radiological study may be summarized as follows: (1) Relatively inert substances—for example, barium emulsion—are capable of producing the post-gastrectomy syndrome. (2) Symptoms may occur before jejunal filling has begun. (3) There is no significant difference in the incidence of rapid emptying, delayed emptying, and afferent-loop filling between cases with and those without the early post-gastrectomy syndrome. (4) There is a greater descent of the gastric stoma in changing from the supine to the erect position in cases with the syndrome than in those without (Table III). The interpretation of this observation, assuming the gastro-oesophageal junction to be fixed, is that it represents stretching of the gastric remnant by the weight of its contents.

TABLE III.—*Comparison of Degrees of Radiological Descent of Stomach in Cases With and Without Symptoms*

Degree of Descent	With Symptoms	Without Symptoms
0–3 cm.	5 (8%)	68 (72%)
3–5 ,, ...	16 (26%)	27 (28%)
5–7 ,, ...	11 (18%)	0
7–9 ,, ...	25 (41%)	0
9–12 ,, ...	4 (7%)	0
Total	61	95

C. Studies of Glucose-tolerance Curves

Glucose-tolerance tests using capillary blood were performed on all cases as a routine. The findings are summarized in Table IV; this shows no significant difference in the variations of the blood-sugar level in patients with the early syndrome and those without it.

TABLE IV

	Cases With Syndrome	Cases Without Syndrome
Average maximum blood sugar ..	152 mg.	149 mg.
,, minimum ,, ,, ..	73 ,,	74 ,,
,, fall	79 ,,	78 ,,
,, rate of fall	2 mg./min.	1·8 mg./min.

D. Effect of a Mercury-loaded Bag in the Gastric Remnant

The findings which suggested this experiment were as follows: (1) The clinical fact that it was the heaviest meal of the day that produced the syndrome most frequently; (2) change of posture—that is, from the erect to the supine position—afforded marked relief; (3) the fact that relatively inert substances—for example, barium—produced symptoms identical with the postcibal syndrome; (4) the radiological finding that cases with the syndrome showed a greater descent of the stoma than did asymptomatic cases.

In this test on cases of the early syndrome the patient was asked to swallow a Miller–Abbott tube, after which he was examined radiologically to verify the position of the tube and the bag. With the patient lying in the supine position, a measured amount of mercury was introduced into the bag via the tube. The weight of mercury corresponded to the weight of the meal which normally produced symptoms. A weight of 12 oz. (340 g.) corresponded to 25 ml. of mercury. When this was done the patient assumed the erect position and the effects were then recorded.

(*a*) In 49 patients (80%) there were no symptoms in the supine position. The remaining 12 patients noted some heaviness in the epigastrium only.

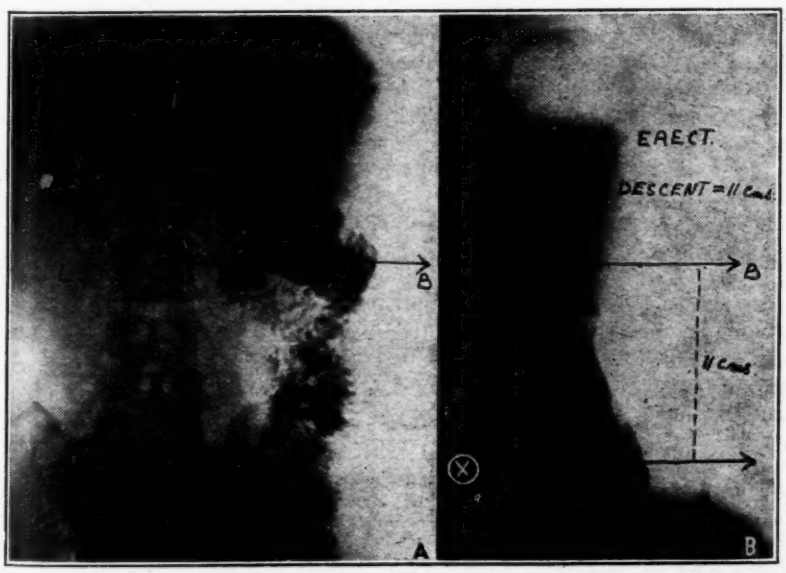

FIG. 2.—Illustration of descent of the stomach with change from (A) the supine to (B) the erect position (descent = 11 cm.).

(b) On assuming the erect position, 57 patients (93%) complained of heaviness and fullness in the epigastrium—high in the costal angle. This was associated with nausea, and six patients began retching. All showed increased pulse rate, pallor, and sweating, whilst 24 complained of palpitations and a feeling of suffocation. Two patients fainted in assuming the erect position, and no further tests were carried out on them. On returning to the supine position these symptoms disappeared in five to ten minutes.

(c) Patients with retrocolic anastomoses required more mercury to produce symptoms compared with those with antecolic anastomoses (Table V).

TABLE V.—*Comparison of Mercury-bag Test in Short Loop and Long Loop Anastomoses*

	Retrocolic—Short Loop	Antecolic—Long Loop
Weight of mercury to produce symptoms (mean)	10 oz. (283 g.)	6–7 oz. (170–200 g.)
Amount of bile-stained fluid aspirated in supine position (mean)	6–10 oz. (170–284 ml.)	9–20 oz. (255–568 ml.)
Weight of additional mercury to produce symptoms (mean)	3 oz. (85 g.)	5–6 oz. (142–170 g.)

The experiments were then repeated on 59 patients—that is, excluding the two patients who reacted so markedly to the previous test. On this second occasion, however, the patients were instructed to lie supine half an hour before the test was begun. During this time the Miller–Abbott tube was still in position and aspiration was carried out. Bile-stained fluid was readily aspirated in amounts varying from 6 to 23 oz. (170 to 650 ml.). The same weight of mercury as in the previous test was then reintroduced into the bag, the patient still being supine. On adopting the erect position 10 patients had symptoms exactly as before. It was noted that these patients were those in whom small amounts of bile were aspirated. In four cases the patients complained of heaviness in the epigastrium, but there were no other symptoms—no vasomotor features. In the remaining 45 cases (76%), however, there were no symptoms until a further amount of mercury was added to the bag. This weight of extra mercury varied from 2 to 7 oz. (57 to 200 g.). To complete the test about 2 oz. (57 ml.) of barium emulsion was given to verify radiologically that the bag had not passed through the stoma during the course of the test.

Finally, the response to splanchnic block was observed. Of 53 patients on whom this was tried, 41 (77.3%) were free from symptoms when the loaded bag was in position. In seven patients, although there was a fall in blood pressure, indicating adequate nerve block, symptoms still occurred, but of reduced severity.

Throughout these tests two points were constantly checked. First, care was taken that the weight of the mercury was not taken up by the tube, so preventing full traction on the stomach. In each case about 18–24 in. (45–60 cm.) of the tube was allowed to coil up in the gastric remnant, and when the mercury was introduced the tube was held vertically so that all the mercury entered the bag or the immediately adjoining part of the tube in the stomach. Secondly, when the mercury was aspirated the same volume of saline was introduced into the bag. In no case did this cause symptoms. This was done to ensure that it was not the distension of the bag in the gastric remnant that caused symptoms during the tests.

It must be stressed that this test is very difficult to perform at times. The loaded bag often slips through the stoma and no symptoms are produced. Sometimes the bag slips through the stoma after producing symptoms, and in these instances the symptoms disappear at once.

The average weight of mercury required to produce symptoms in this series was 8 oz. (227 g.). In the 95 controls this amount of mercury failed to produce effects in any of the cases, but 14 oz. (400 g.) produced identical symptoms in approximately 74%. In a series of six people who had never had a gastrectomy, 10% got symptoms similar to the early syndrome when 14 oz. was put into the bag.

Comment.—This seems to be the most significant test of the series. It indicates that a major factor in the production of the early syndrome is the weight of food in the stomach. It also indicates that the weight of the contents of the afferent loop and the weight of a meal in the stomach are complementary. If the afferent loop is relatively empty a greater bulk of meal can be taken before symptoms occur. If, on the other hand, the loop is heavy with temporarily retained contents a small meal increases the whole weight to the critical level required to produce symptoms.

E. The Therapeutic Value of Splanchnic Block

Splanchnic block by the posterior route (Kappis) was used many times during the whole series of investigations. Initially, successful block was obtained in less than half the cases to which it was administered. Recently, however, success has been obtained in about three-quarters of all attempts made. The effect of splanchnic block has been observed now on all 61 cases—some after one injection (that is, apart from splanchnic block in the experiments) others after two or even three injections. The success of the block was judged by the associated fall in the blood pressure.

In four cases the patients have had no further trouble—the longest period being seven months. In 46 cases the patients were relieved for periods ranging from two to nine days. During this time they were able to eat bulky meals, which they had not been able to do since the operation. In the remaining 11 patients the block failed to abolish the syndrome. This particular finding will be discussed in a later paper dealing with the nerve pathways involved. All that is necessary at the moment is to say that splanchnic block relieves only those cases in which all the afferent fibres involved pass through the splanchnic plexus. It is well known that in a proportion of cases some fibres go direct to the splanchnic nerves and lower thoracic ganglia. These cases will therefore not be affected by splanchnic block.

Distilled water was used for the second injection in eight cases, but without effect.

It would appear that the early post-gastrectomy syndrome is transmitted via the sympathetic system. In a personal communication in 1949 Hastings-James stated that sympathectomy would relieve symptoms; and at the last Gastro-enterological Conference in the U.S.A. it was stated that "etamon" was also effective in relieving the symptoms.

Conclusions and Discussion

In view of the above we are able to draw the following conclusions:

1. The symptoms constituting the syndrome are not all due to the same cause. The sensation of central

abdominal fullness is due to the distension of the jejunum. The rate of emptying of the gastric remnant and thus of jejunal filling—that is, the *x*-ray observation that led to the use of the term "dumping"—is a factor in the production of the sensation of fullness, but is unrelated to the rest of the syndrome. Indeed, fullness is not the most distressing part of the syndrome. It is the vasomotor upset—that is, the feeling of warmth, sweating, tachycardia, palpitations—which really distresses the patients, and these symptoms were not reproduced by jejunal distension.

2. The vasomotor component can be completely reproduced by inert substances—that is, both barium and a mercury bag in the gastric remnant.

3. There is no difference in the blood-sugar curve of those with and without the early syndrome.

4. The afferent-loop reflux *per se* is not a cause of the symptoms, because, as has been shown, the incidence of this finding is equal in cases with and without the syndrome.

5. The syndrome can be reproduced fully by a mercury-loaded bag in the gastric remnant, where the weight of the mercury is roughly equal to the weight of a meal known to produce symptoms. This test also suggested that the weight of the gastric contents plus the weight of the contents of the afferent loop are complementary factors in production of the syndrome.

6. If the patient lies down the vasomotor symptoms produced by the mercury bag are abolished. On the other hand, posture had no effect on the sensation of fullness produced by balloon distension of the jejunum.

7. Splanchnic block suggests that the syndrome is mediated by the sympathetic rather than the vagus nerves.

As a result of these studies it appears that several different mechanisms are involved in production of the syndrome—namely, jejunal distension producing a sensation of fullness, and drag produced by the combined weight of the gastric and afferent-loop contents in the erect posture leading to vasomotor effects. Experimentally it has been shown that abolition of the effect of gravity abolishes the latter but not the former. This corresponds with the clinical observation that lying down during an attack causes the vasomotor symptoms to disappear within five minutes, whereas the sensation of fullness may persist for an indefinite period.

In a subsequent paper we hope to present a clinical study of the problem and attempt to correlate it with these experiments.

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THYROID ACTIVITY IN MENTAL PATIENTS

EVALUATION BY RADIOACTIVE TRACER METHODS

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The radioactive tracer method of estimating thyroid function used in these investigations has been reported elsewhere (Haigh and Reiss, 1950; Reiss *et al.*, 1951). Only small doses of radio-iodine are employed, and the method does not depend upon absolute measurements in the thyroid region. The index of thyroid function is calculated from measures of the uptake by the thyroid and of the urinary excretion of radio-iodine. With the particular units chosen, normal values of this function, I_t, have been found to lie in the range—males 1.8 to 8, females 3 to 12. The error in the measurements is about ±20%, and there is evidence that the spread of the chosen normal limits is probably too great. It has been found useful to divide each normal range into an upper and lower normal range about the mean normal value.

The investigation can be repeated after two to four weeks without danger to the patient and without error due to the earlier injection. The radiation from the small dose (25 μc.) of radio-iodine appears unlikely to influence thyroid function, which may be a source of error in methods employing large doses such as that published by Bowman *et al.* (1950) in his survey of 49 psychiatric cases.

Our series consists of 541 cases in an acute psychiatric admission hospital and out-patient clinic, embracing most of the usual psychiatric disorders. The series includes many cases of mental illnesses of recent origin and short duration, and is a fair cross-section of psychoneurotic and psychotic illness.

The Tables show the distribution of the psychiatric categories according to the degree of thyroid activity. Abnormal thyroid values do not seem to be consistently characteristic of any single psychiatric disorder,

TABLE I.—*Male Patients*

Ranges I_4	Characterization of Range	Objective Anxiety	Depression	Mania	Recent Schizophrenia	Chronic Schizophrenia	Other Psychiatric Disturbances
		No.	No.	No.	No.	No.	No.
0–1·8	Underfunction	28 (44%)	20 (24%)	1 (20%)	8 (33%)	15 (17%)	6 (17%)
1·8–3·6	Lower normal range ..	25 (39%)	17 (20%)	3 (60%)	5 (21%)	21 (24%)	9 (26%)
3·6–8·0	Upper normal range ..	8 (12%)	25 (30%)		5 (21%)	31 (36%)	9 (26%)
8·0–100	Overfunction	3 (5%)	22 (26%)	1 (20%)	6 (25%)	20 (23%)	11 (31%)
	Total (299)	64	84	5	24	87	35

TABLE II.—*Female Patients*

Ranges I_4	Characterization of Range	Objective Anxiety	Depression	Mania	Recent Schizophrenia	Chronic Schizophrenia	Other Psychiatric Disturbances
		No.	No.	No.	No.	No.	No.
0–3	Underfunction	6 (15%)	28 (23%)	1 (20%)	2 (10%)	2 (11%)	5 (12%)
3–6	Lower normal range ..	2 (5%)	29 (24%)	1 (20%)	2 (10%)	10 (55%)	12 (29%)
6–12	Upper normal range ..	15 (38%)	49 (41%)	2 (40%)	6 (30%)	6 (33%)	18 (44%)
12–100	Overfunction	16 (41%)	13 (11%)	1 (20%)	10 (50%)		6 (15%)
	Total (242)	39	119	5	20	18	41

but analysis shows that: (1) In male anxiety there was underfunction in 44% and functions in the lower part of the normal range in 39% of the cases. Thus in 83% of male anxiety there was a tendency towards reduced thyroid function. (2) In female anxiety, by contrast, 41% are above normal and 38% are in the upper normal range: a tendency to hyperfunction in 79%. (3) In acute female schizophrenia the distribution was similar to female anxiety, with 50% hyperthyrotic, but hyperfunction was not observed in any case of chronic female schizophrenia. (4) There was no tendency to hyperfunction in acute male schizophrenia. (5) In other categories the level of thyroid function did not seem to be significantly related to the psychiatric disorder alone.

Discussion

The method employed seems capable of detecting slight degrees of thyroid hyper- or hypo-activity with a precision hitherto unobtainable, and therefore of analysing the so-called borderline cases. Thyroid abnormality may be an important factor in the production of mental illness (Asher, 1949; Simpson, 1949), but probably because of variable aetiological factors there is no psychiatric reaction characteristic of hyper- or hypothyroidism alone. This is in agreement with the experience of Means (1948) in general medicine. Hypo- and hyper-thyroidism diagnosed on clinical evidence are uncommon in average psychiatric case material.

However, there are indications of thyroid disturbance in schizophrenia, and a low B.M.R. has been reported by Bowman and Fry (1925), Hoskins and Sleeper (1929, 1932), and Hoskins (1946). According to the last-named some schizophrenic patients can tolerate up to 60 gr. (4 g.) of thyroid daily. We have found the same, and regard it as a consequence of under-sensitivity of the body tissues to thyroid hormone and not a sign of hypothyroidism. This may be comparable to the well-known insulin resistance observed in schizophrenia. Further evidence of insensitivity of peripheral tissue in schizophrenia is provided by the paradox cases reported elsewhere (Reiss *et al.*, 1951) in which increased thyroid activity is associated with a low oxygen consumption. The paradox reaction has in some cases been abolished and the B.M.R. brought up to normal, or increased, by treatment with vasodilating drugs, which presumably facilitated the action of thyroid hormone on peripheral tissues.

The differential diagnosis between anxiety states and hyperthyroidism has always been difficult to make from clinical evidence. The tracer method allows this problem to be studied. The significant incidence of hypothyroidism noted in male anxiety was unexpected. Animal experiments carried out in this laboratory have shown that small doses of adrenaline infused simultaneously (2 μg./min.) with the radio-iodine inhibit the uptake of the latter by the rabbit thyroid. By analogy we imagine that in male anxiety, when adrenaline is mobilized by frequent psychological stimuli, a state of functional hypothyroidism is created, depending to a great extent on the severity and chronicity of the neurosis. This may explain why chronic anxiety in males even of good personality is often uninfluenced by psychotherapy, for it is probable that prolonged hypothyroidism affects brain metabolism, impairing efficiency and adaptability.

In female anxiety the tendency to a higher rate of thyroid function may be a constitutional attribute linked to the emotional reactions peculiar to the normal female, or there may be some fundamental difference between male and female anxiety neurosis, or it may be due to the female endocrine system.

Many investigators have treated psychotic patients with thyroid with inconclusive results. On the indications of the tracer method, thyroid treatment should be examined afresh. Bearing in mind that, according to animal experiments, the brain is extremely resistant to thyroid hormone, treatment may have to be prolonged, with high doses. Our results so far in chronic anxiety and psychotic material selected and controlled by the tracer method have been encouraging.

Summary

The thyroid activity of 541 psychoneurotic and psychotic patients has been evaluated, using a radio-iodine tracer method.

In over 50% of male anxiety, thyroid activity was subnormal.

In female anxiety, thyroid function was usually hypernormal.

In acute female schizophrenia, thyroid function was usually increased, but was normal or subnormal in the chronic form.

There were no psychiatric reactions characteristic of thyroid abnormality.

The significance of the findings and the possibility of thyroid therapy have been discussed.

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ACUTE UNILATERAL DACRYOADENITIS

A REPORT OF FOUR PATIENTS

BY

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During the six months October, 1949, to March, 1950, four cases of acute dacryoadenitis were observed among the 3,622 new ophthalmic patients at the General Infirmary at Leeds. This incidence contrasts with the views of many writers who regard it as a rare condition, and several articles describe a single case which is reported by virtue of its rarity. Arlt (quoted by Schirmer, 1877) stated that he had never met a case. Pooley (1884) stated that the condition was rare and reported one instance which was considered to be metastatic in origin, though at the time there was a diphtheritic infection of the conjunctiva of the other eye. Galezowski (1886) also stressed its rarity, but stated that he had met five examples. Weeks (1911) reported the incidence to be 1 in 10,000 ophthalmic cases. Richardson (1942) was able to compile from the literature 37 cases of gonococcal origin and mentioned the causes of acute dacryoadenitis which had been reported.

The clinical features of the four patients with acute dacryoadenitis are described below, and points of particular interest are discussed.

Case 1

Five weeks before admission this patient, a girl aged 16, had had what was thought to be influenza, which lasted two weeks. She made an apparently complete recovery and was able to resume work. The day before admission a painful swelling appeared in the upper lid of the left eye and was accompanied by malaise and lack of appetite.

On examination the patient was rather lethargic. Her temperature was normal, pulse 80, respirations 18. There was no cough, and the chest condition seemed normal. Radiologically the paranasal sinuses appeared normal.

Ocular Condition.—A swelling was seen in the upper lid of the left eye, situated mainly at the outer aspect but extending to involve the whole lid and adjacent frontal region. The swelling was tense and tender; the eye was considerably proptosed, but there was only slight chemosis of the bulbar conjunctiva. Eye movements were almost absent. A radiograph of the sinuses showed no evidence of infection.

Systemic administration of penicillin and sulphanilamide was accompanied by the instillation of penicillin drops and application of heat to the eye. After a few days the swelling became less tense and subsided, allowing palpation of a firm lump in the upper lid which was felt to extend forwards from under the superior orbital margin. The general condition improved as the swelling diminished. When the patient was seen after four weeks no lump could be palpated and the chemosis had disappeared, but there was still slight ptosis and some weakness of the left superior rectus.

Case 2

Three weeks before attending hospital this patient, a boy aged 10, had had what was thought to be tonsillitis, for which he was confined to bed for one week. He made an apparently complete recovery and was able to resume school. Four days before admission a painful swelling appeared in the right upper lid, accompanied by considerable malaise and loss of appetite. One intramuscular injection of penicillin had been given by his own doctor.

On examination his general state was one of languor and apathy. His temperature was normal and pulse 80. The patient had a loose cough, and rales and rhonchi were heard in the chest. Radiological examination revealed some haziness of the paranasal sinuses.

Ocular Condition.—The right upper lid was swollen. This swelling was mainly in the outer part, but involved the whole lid and extended into the frontal region. It was tense and tender and there was complete ptosis. The eyeball was considerably proptosed, the conjunctiva was chemotic and bulging between the lids. Movements of the eye were almost absent. Acute tenderness was felt on palpation over the right malar bone. Both fundi appeared normal. Radiologically there was thickening of the mucosa of the frontal sinuses; this was not considered an adequate cause for the swelling of the lid.

Systemic administration of penicillin and "sulphatriad" was accompanied by instillation of penicillin drops and the application of heat to the eye. Next day the pulse rate had increased to 90 though the temperature remained normal, so an incision was made over the swelling and forceps were inserted. No pus appeared until the orbital septum had been pierced, when about 0.5 ml. of creamy pus was evacuated. During the next seven days the swelling and proptosis subsided and a lump could be palpated in the upper lid. This lump was felt to extend forwards from under the superior orbital margin. When the patient was seen five weeks later there was a complete recovery of both the general and the local condition.

Case 3

A girl aged 16 had recently had an attack of what was considered to be influenza. She was in bed for one week and then returned to school for two weeks. Four days before she attended hospital a painful swelling appeared in the upper lid of the left eye, mainly at the lateral aspect. The swelling increased during the next few days and was accompanied by ptosis and chemosis.

On examination her general condition was one of languor and malaise. Her temperature and pulse were normal.

Ocular Condition.—The left eye showed complete ptosis, with a tender tense swelling occupying the upper lid, mainly in its outer part and extending into the forehead. There was considerable chemosis, mainly of the lateral bulbar conjunctiva. Slight proptosis was present and movement of the globe was limited in all directions. Radiological examination revealed no evidence of infection of the paranasal sinuses.

Systemic administration of penicillin and sulphatriad was accompanied by the instillation of penicillin drops and the application of heat to the eye. The swelling subsided gradually, and after four to five days a lump became

palpable in the lateral part of the upper lid, emerging from under the superior orbital margin. Apart from some nausea from sulphatriad, the general condition improved as the swelling diminished. Two weeks later the proptosis had disappeared, but there was some diplopia on looking to the left. The diplopia was the last to clear up and was still noticeable after five months.

Case 4

A boy aged 14 began to complain of headache and feverishness six days before attending hospital. Three days later he had a painful swelling of the upper lid of the right eye and, at the same time, a sharp pain in the left side of the chest. He was seen by his doctor, who was doubtful whether to diagnose right frontal sinusitis or left lower lobe pneumonia. His temperature exceeded 100° F. (37.8° C.) during the next few days.

On examination signs of consolidation with a small effusion were found at the left base of the chest. A blood count showed 8,600 white cells with 81% polymorphs. There was

a swelling of the right upper lid, maximal at the lateral aspect but involving the whole lid and extending into the frontal region (see illustration). The swelling was tense and tender and was associated with complete ptosis, some proptosis, and chemosis. Movements of the right eye were considerably diminished in all directions but mainly upwards and outwards. The right malar bone was tender on palpation.

Systemic administration of penicillin and sulphadimidine was accompanied by the instillation of penicillin drops and by the application of heat to the eye. Aspiration of the pleural effusion was unsuccessful. During the following week complete resolution occurred at the left base, but no fluid was found, though transient inflammatory changes appeared at the right base, accompanied by fever. With treatment the swelling in the right lid gradually subsided during the course of seven days, and a lump became palpable in the lateral part of the upper lid. Three weeks later there was only slight ptosis and slight thickening of the outer part of the lid.

Discussion

The diagnosis of infection of the lacrimal gland depends upon the palpation of a lump in the lateral part of the upper lid, extending forwards into the lid from under the outer aspect of the supraorbital margin; therefore the posterior limit of the lump cannot be determined, though the anterior edge is easily palpated through the thickness of the lid. During the initial stages of the infection the tenseness and tenderness of the region prevent any useful palpation, but the condition may be suggested by a swelling which is maximal at the lateral aspect of the lid. Such a swelling must be distinguished from other inflammatory swellings of the upper lid.

The most important conditions which may simulate acute dacryoadenitis are orbital cellulitis, osteitis, and acute inflammation of the Meibomian gland. Schirmer (1877) stated that many instances described as infection of the gland were really infections of the cellular tissues in the vicinity.

Orbital cellulitis arising from metastatic infection, from spreading thrombophlebitis, or by direct spread from a paranasal sinus usually produces a swelling which is diffuse throughout the length of the lid or maximal at the nasal aspect. Ethmoidal mucocele typically produces a swelling which is at the medial aspect of the lid and displaces the eye laterally and downwards (Thomson and Negus, 1948).

Osteitis of the frontal bone may produce a swelling of the upper lid, but radiological changes in the bone would be expected, and such a subsiding osteitis would be unlikely to leave a lump at the site of the lacrimal gland. Benford and Brunner (1947), however, give details of a patient with a polypoid mass of sinus mucosa which had herniated through a fistula in the frontal bone.

Acute infection of a Meibomian gland may cause a swelling in the lid and on subsiding may leave a firm lump; the lump is likely to be confined to the lid and not to extend under the orbital margin; moreover, eye movements are not likely to be affected.

Some interesting features are presented by these four patients. In each there was an infection of the respiratory tract. The first three gave a history of such an infection two to three weeks before attending hospital and apparently had made complete recovery. Two of these febrile attacks had been ascribed to influenza and one to tonsillitis. The fourth patient apparently acquired infection of the lung and of the lacrimal gland simultaneously. Why infection of the lacrimal gland should have this association with infection of the respiratory tract is difficult to explain. It may be that the gland infection follows transport by the blood stream of material from a site of infection elsewhere in the body, and a common site for such an infection is the respiratory tract.

General symptoms were severe in the early stages. By the time the patients were seen in the eye department, all had had penicillin systemically and their temperature was normal; nevertheless there was considerable malaise and loss of appetite. Recovery of the general condition seemed to run concurrently with subsidence of the swelling, in contrast with the type of infection described by Toulant, Benhamou, and Foissin

(1947) in which the local condition cleared up in a matter of days but the general malaise was considerably prolonged.

Acute tenderness caused by pressure over the zygoma was noticed in Case 2, and thereafter was elicited in Cases 3 and 4. It was not noticed in Case 1, perhaps because that area was not palpated, but in Case 2 the provisional diagnosis of osteitis of the zygoma was made, owing to the situation and degree of the tenderness. This point was about 1 in. (2.5 cm.) behind and below the external canthus—a point quite distinct from that found in tenderness due to enlarged preauricular gland—and presents an interesting feature for speculation. It may be that the sensory nerve supply for this area of skin is derived from the zygomatic branch of the maxillary nerve, and as a result of the communication between the lacrimal and zygomatic nerves tenderness in this region reached a high degree. No reference to this phenomenon could be found in the literature, yet it appears to be characteristic of acute dacryoadenitis at an early stage, when swelling of the lid is too tense to permit palpation of a lump.

Ptosis was present on each occasion, and owing to the situation of the swelling, which was maximal at the lateral aspect of the lid, a sinuous outline was given to the lid margin. This appearance has been noted by Richardson (1942) and by Rosen (1944).

Restriction of eye movement was found in all patients in the early stages of the gland infection; in two it amounted to almost complete immobility of the eye, and a notable feature was the comparative slowness in recovery of full eye movements.

Proptosis was a pronounced feature in one instance. This patient had had the most severe general reaction, and one might visualize an abscess in the gland which had extended backwards to cause an orbital cellulitis.

Chemosis was seen in all patients, chiefly affecting the temporal bulbar conjunctiva. In two it caused bulging of the conjunctiva between the lid margins.

In conclusion, it may be stated that acute dacryoadenitis is not uncommon in some districts and at certain times of the year. Schmidt (quoted by Schirmer, 1877), stated that the condition was not uncommon; Wright and Nayar (1937) described three cases which seemed to be caused by *Diplobacillus morax-axenfeld*. Epidemics have been reported from time to time (Galezowski, 1875; Groenouw, 1889 (quoted by Nicolau, 1933); Nicolau, 1933; Toulant, Benhamou, and Foissin, 1947). The seasonal incidence is a matter of some interest; Nicolau described 10 cases which occurred during the winter months, and, on investigating 81 instances previously reported, she found an increase in numbers during the months of October to March, those months in which respiratory infection is most common. Respiratory infection may be a frequent cause of unilateral acute dacryoadenitis.

It appears that there may be a latent interval of two to three weeks during which the patient feels quite well before orbital symptoms become manifest; only careful history-taking will reveal that there has been a period of headache, malaise, sore throat, and feverishness. Fralick (1935) makes the following comment: "Seldom is the practising ophthalmologist called upon to treat conditions affecting the lacrimal gland. Consequently, little is written in the standard textbooks on the subject of acute inflammation of this structure. It is therefore conceivable that a few cases may leave our offices improperly diagnosed because of our unfamiliarity with this particular group."

Summary

Four patients with acute dacryoadenitis have been seen during a six-months period. The clinical features are described and discussed. Attention is drawn to the following points: (1) the rarity of acute dacryoadenitis, (2) its association with respiratory infection, (3) its seasonal incidence, and (4) an early diagnostic sign of acute dacryoadenitis consisting of tenderness over the malar bone.

I would like to thank Dr. Maxwell Telling for much valuable criticism and for access to Case 4, and Mr. John Foster and Mr. George Black for their help and for allowing me to describe their patients.

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BORNHOLM DISEASE

BY

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Outbreaks of Bornholm disease have been described in this country at infrequent intervals since the work of Pickles (1933) in Yorkshire. The subject was recently reviewed by Hopkins (1950), who reported a further series of cases; and the possible connexion between this disease and the Coxsackie group of viruses was discussed by Findlay and Howard (1950). Very shortly after the publication of the latter two papers a small group of patients attended this hospital with clinical histories corresponding closely to those reported in previous descriptions of Bornholm disease. Dr. G. M. Findlay very kindly attempted to isolate Coxsackie virus from the nasal washings of some of the patients and to carry out the serological antibody reactions on them from the earliest stages of the outbreak. The clinical histories of these patients are briefly described, together with a summary of Dr. Findlay's findings.

Case Reports

Case 1.—A girl aged 18 first noticed mid-thoracic pain and pain behind the right shoulder on May 28, 1950. It was worse on inspiration but was not severe, and she did not mention her symptoms until three days later, when two

other members of her family had been similarly affected. She was found to have a temperature of 101° F. (38.3° C.), but the fever settled within two days, and she was then free of all symptoms. This girl did not attend hospital at any time and so no investigations could be carried out on her. A fortnight later, however, she was reported to be completely well.

Case 2.—On May 29 a schoolboy aged 14, a brother of Case 1, complained of a stabbing pain on the left side of the chest on inspiration. He had previously had a heavy head cold for a few days but had had no other symptoms. The onset of his pain was quite abrupt while he was sitting in a chair. On admission his respiration was shallow and was obviously causing pain. His temperature was 104.4° F. (40.2° C.), pulse 110, and respirations 28. Movement and air entry on the left side of the chest were diminished and a friction rub could be heard over a small area in the front of the chest, just to the left of the sternum. No other abnormal physical signs were found. No chemotherapy was given, and within a day the pleural rub had gone, though the pain on inspiration persisted; on the second day he developed epigastric pain on respiration. The temperature was 101.4° F. (38.55° C.) on June 1 and then slowly settled to normal during the following week. A blood count showed: haemoglobin, 80%; leucocytes, 9,000 per c.mm. (69% polymorphs, 25% lymphocytes, 6% monocytes). The sedimentation rate was 15 mm. in the first hour. A chest radiograph showed no abnormality. The patient was discharged perfectly fit on June 19.

Case 3.—On May 30 another brother of Case 1, aged 12, complained of epigastric discomfort, headache, and general malaise, and was found to have a temperature of 101° F. (38.3° C.). Later in the day he developed a sharp pain in the left upper chest, which, though not severe, was increased by deep breathing. On the next day his chest pain was worse and his abdominal pain was also exacerbated by breathing, so he was admitted to hospital. On admission he was hot and flushed but not unduly distressed. His temperature was 100.6° F. (38.1° C.), pulse 110, and respirations 26. A few lymph nodes were palpable in both axillae, but no other abnormal physical signs were found in the chest or elsewhere. Within a day his pain had gone and the temperature settled after a further three days. A blood count showed: haemoglobin, 78%; leucocytes, 9,000 per c.mm. (neutrophils 45%, lymphocytes 38%, monocytes 14%, eosinophils 3%). The sedimentation rate, uncorrected, was 21 mm. in the first hour. A chest radiograph was clear. He was discharged fit on June 10.

Case 4.—On June 1 a married sister aged 21 complained of cough and of sharp pain in the right side of the chest and behind the lower end of the sternum. The pain was increased by deep breathing and by coughing. She felt feverish all that day, and was still feeling ill three days later. Despite this she attended hospital to visit her brothers and was examined there. She then had a temperature of 99.6° F. (37.55° C.), but no other abnormality was found on physical examination. As she was breast-feeding her 5-weeks-old infant it was impossible for her to come into hospital, but she was seen again on subsequent visits to her brothers. Although on her second visit on June 11 the fever and pain had settled, she still felt unwell, but further physical examination again revealed no abnormality and the chest radiograph was clear. This patient did not feel completely well for a further three weeks.

There were seven members of this family. The mother, aged 43, shared a room with a son aged 4, and Case 1. Case 2 shared a second room with a 12-year-old brother. Case 3 shared a room with a 7-year-old adopted brother. Case 4 and her baby lived in a near-by flat, her husband at the time of the outbreak being away from home. Case 4 was a daily visitor to her family. It is curious that only one occupant of each room was affected, whereas, in the outbreak reported by Hopkins, every member of two affected households had symptoms of the disease.

Case 5.—On June 11, 10 days after the admission of Case 3, a boy aged 7½, who had been admitted on May 26 with a boil on the arm and who occupied a bed next to Case 3, developed a sudden spike of fever of 102° F. (38.9° C.) and complained of pain in the left side of his chest increased by inspiration. On examination the respiration rate was 24 and the pulse rate 120. There was diminution of movement and air entry on the left side of the chest, but there was no friction rub nor any other abnormal findings. His temperature was still 99.6° F. (37.55° C.) on June 13, but settled completely, and he was perfectly well when discharged on June 16. On June 12 a blood count showed: haemoglobin, 90%; leucocytes, 7,000 per c.mm. (neutrophils 55%, lymphocytes 20%, eosinophils 12%, basophils 2%, monocytes 10%, plasma cells 1%). The sedimentation rate, corrected, was 18 mm. in the first hour. A chest radiograph was clear. The patient attended hospital on August 22; he then felt perfectly well and a chest radiograph was again normal.

Case 6.—A boy aged 16, the last patient in this series, had no connexion with any of the earlier cases nor was there a history of contact with anyone else with a similar illness. Although the serological investigations were negative, the course of his illness was so like that of the others that he is included in the series. He was admitted on June 16 with a one day's history of pain across the upper part of the chest, worse on deep inspiration, and of epigastric pain. During that time he had also noted nausea and anorexia and frontal headache, but had not vomited. On examination his temperature was 102° F. (38.9° C.), pulse 95, and respirations 24. Palpable glands were present in the posterior triangle of the neck on both sides. There was tenderness to palpation right across the lower abdomen. No abnormalities were detected in the chest or elsewhere. Investigations: haemoglobin, 98%; white cells, 6,000 per c.mm. (neutrophils 65%, lymphocytes 28%, monocytes 6%, eosinophils 1%). A blood count on June 30 was substantially the same. The Mantoux intradermal test was positive at a dilution of 1:1,000, and a chest radiograph was normal. This patient ran a swinging pyrexia until June 25, after which he settled down completely and was well on discharge on July 5.

No meningeal or paralytic signs were observed in any case in this series.

Further Investigations

Attempts were made to isolate Coxsackie virus from the nasal washings of Cases 2, 3, and 4. The results were negative in the first two cases, but the virus was isolated in the nasal washings from Case 4 on the second day of her illness.

The complement-fixation reactions against Coxsackie virus 2 were as follows:

	Day of disease	Titre
Case 4	2	Negative
	5	1:10
	18	1:20
Case 3	3	1:5
	6	1:10
	19	1:20
Case 2	2	1:5
	5	1:5
	18	1:10
Case 5	3	1:5
	77	1:10

One of the contacts gave a titre of 1:10 during the first and third weeks after the outbreak, but the other two members of the family who were tested never showed a titre greater than 1:5.

Case 6 gave negative results on the second and nineteenth days of his illness.

Discussion

These six patients all had clinical histories and findings which were essentially similar, and which, furthermore, closely resembled previous descriptions of Bornholm disease. The condition was in fact suspected on the admission of Case 1 even before the occurrence of further cases in the family helped to establish the diagnosis. The first five patients, forming as they did a small group, could be fairly confidently diagnosed as suffering from Bornholm disease. In these cases the connexion previously described between Bornholm disease and Coxsackie-virus infection (Curnen, 1950) was confirmed by the isolation of virus in one case and by a rising agglutination titre in all four of the five patients who were available for testing; no such confirmation was obtained in Case 6, and the final diagnosis of this patient cannot be regarded as established.

Coxsackie virus was first isolated from two paralytic patients during an epidemic of poliomyelitis (Dalldorf and Sickles, 1948). During 1947 and 1948 there were reports from the United States of various outbreaks of febrile illness in which many cases resembled non-paralytic poliomyelitis. In some of these cases poliomyelitis virus was isolated, but in others faecal specimens and nasopharyngeal washings tested for poliomyelitis virus were non-infective for monkeys (Dalldorf, 1950). During these outbreaks Coxsackie virus was isolated from patients with various minor illnesses, with illness resembling epidemic myalgia (Bornholm disease), and with illness suggesting non-paralytic poliomyelitis. In some but not all of the last group poliomyelitis virus was also isolated (Curnen, 1950).

In some previously reported cases of Bornholm disease signs of meningeal irritation have been noted. DeRudder (1937) drew attention to the similarities between epidemic myalgia and poliomyelitis, although his views were to some extent disputed by Lindberg (1938). The similarities were also stressed more recently by Ronse (1949).

There is of course no reason why patients should not harbour both poliomyelitis and Coxsackie virus at the same time, and this association has in fact been recorded (Melnick, 1950).

The similarities and differences between these two groups of virus are summarized by Melnick (1950), who concludes that, though antigenically distinct, their biological behaviour is surprisingly similar. He points out, furthermore, that members of the Coxsackie group of viruses are now being repeatedly found where poliomyelitis is epidemic.

I am grateful to Drs. H. V. Morlock and E. W. Hart, under whose care these patients were treated, for their permission to publish this article, and to Dr. L. Cohen, who brought four of the patients to our notice. I am also very much indebted to Dr. G. M. Findlay, who carried out all the virological investigations, for his generous assistance.

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TUBERCULOSIS OF LIVER TREATED WITH STREPTOMYCIN

BY

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The following case is of interest on account of its rarity and its clinical course.

Case Report

The patient, a student aged 20, was admitted to hospital on March 14, 1950. He enjoyed good health until June, 1949, and was living in a college pleasantly situated in the country. He noticed, however, that during the first two weeks of his summer vacation in 1949 he was becoming easily tired, could find little energy for his usual holiday activities, and had diarrhoea. Some few days later his stools became very pale and offensive, and he noticed that his eyes "were becoming yellow." A few weeks later he was drenched in a rain-storm, after which severe pain developed in the right loin accompanied by anorexia and malaise. He was confined to bed for seven days, and was seen to be slightly jaundiced. His condition improved with rest, and he resumed his usual activities. Before his return to college in September, however, two of his teeth were extracted; haemorrhage was profuse and persisted over four or five days in spite of plugging. His general condition as a result became very poor.

Lest any absence due to illness should mean the sudden end of his scholastic career, he returned to college, although he felt very weak. He had been advised to take iron, and with this therapy his pallor became less severe. His jaundice persisted, and during the last months of 1949 gradually became more intense. He began to have frequent sweats, often profuse, and especially at night. At the end of December he suffered a minor cut on one of his hands, and again the bleeding was prolonged. A vitamin-K analogue — self-prescribed — made no difference to this tendency to bleed. Bleeding from the gums occurred, becoming more and more frequent until it was a daily event. His appetite at this time was fairly good, and he was passing two or three loose pale motions each day. The urine was deep yellow in colour. He had no cough, and, so far as he could judge, had not lost weight.

His past history was of appendicitis at the age of 7 years and section of peritoneal adhesions at 15, when there was suspicion of mesenteric tuberculous adenitis. No proof of this was ever obtained. The family history shed no light on his illness.

Examination on admission showed him to be a tall lean youth, pale and slightly jaundiced. He was febrile and was sweating freely; his fingers were clubbed; enlarged lymph nodes were not detected. The left elbow-joint was painful and tender, its movements being limited to about a right-angle. The abdomen was distended and the liver slightly enlarged. The spleen and kidneys were not palpated. Examination of the chest disclosed no abnormality, and the cardiovascular and central nervous systems appeared to be normal.

Blood examination revealed an iron-deficiency anaemia: Hb, 76% Sahli (10.64 g.); red cells, 4,580,000 per c.mm.; colour index, 0.8; white cells, 8,000 per c.mm. The differential count gave average readings. The bleeding-time was 4½ minutes by Duke's method, and the coagulation time 8 minutes by the method of Lee and White. The red-cell-fragility test showed commencing haemolysis at a concentration of 0.5% NaCl, complete at 0.35%. The urine contained bile and urobilin. No blood or casts were seen on microscopical examination.

Diagnosis was at this point obscure, and many investigations were carried out. Radiological examination of the

chest showed no evidence of active pulmonary disease. On cholecystography the gall-bladder was considered to be non-functioning. *X*-ray examination of the left elbow-joint revealed no abnormality. The van den Bergh reaction gave a positive indirect result. No serum agglutinins were detected for *Leptospira icterohaemorrhagiae*.

By April, 1950, the left elbow-joint showed the signs of an infective arthritis, and was greatly swollen. Aspiration of the joint revealed pus, and a culture was set up. Epigastric pain was now becoming increasingly severe, and the possibility of impacted gall-stones was considered. The surgeon hesitated to operate on account of the possibility of severe haemorrhage. When the bleeding-time was found to be normal, laparotomy was carried out.

At operation, gall-stones were not found, but the liver was very congested and raw-looking, with numerous small yellow spots all over its surface. Around the liver there were many adhesions to the anterior abdominal wall and viscera. The gall-bladder was normal, but was fixed in adhesions. The head of the pancreas was slightly thickened, but was thought not to be the seat of malignant growth. A piece of the edge of the liver was removed for histological examination.

Three days after operation it became known that from the pus aspirated from the elbow-joint a culture of *Mycobacterium tuberculosis* had been grown. This finding reached startling significance when the pathologist's report on the liver specimen showed that tubercle follicles were present in the liver parenchyma deep to the capsule: tubercle bacilli were not demonstrated, but the lesions were histologically typical of tuberculosis. Also, there was an increase of connective tissue in and between the portal tracts, and the surrounding liver tissue showed irregular hyperplasia and atrophy. The connective tissue contained numerous plasma cells and lymphocytes, and there was pronounced bile-duct hyperplasia. The lesions were summarized as metastatic haematogenous tuberculous follicles, and early scarring resulting from prolonged, or recurrent, and still active infective hepatitis.

Streptomycin Treatment

The problem of diagnosis, of course, now included the possibility of a dual pathology. Nevertheless, it appeared that a case of tuberculosis of the liver had been diagnosed during life without evidence of generalized miliary infection, but with a distant focus which had become manifest long after the initial symptoms of hepatic disorder. Whatever the diagnostic difficulties, there seemed to be no similar therapeutic problem. Streptomycin, which is most successful in some of the rarer manifestations of tuberculous infection, seemed to be the most reasonable basis for treatment. It was first given on May 12, 2 g. daily being injected intramuscularly for the first five days, after which the daily dose was 1 g. This was continued until August 22, when a total of 107 g. had been given.

During the months of treatment the temperature, which previously had shown intermittent elevation, gradually settled and general clinical improvement began. Appetite improved steadily and there was a sustained increase in weight, though bile persisted in the urine, stools remained rather pale, and a tinge of jaundice was perceptible. The erythrocyte sedimentation rate was thought to be a useful index of progress, Westergren's method being used throughout. From the high first-hour reading of 95 mm. on April 18 a steadily continuous fall was observed. On August 27, five days after the cessation of streptomycin administration, the comparable reading was 15 mm.

The tuberculous arthritis of the left elbow-joint was treated by immobilization in plaster. During May the joint became unstable, and two months later was almost completely disorganized. A cold abscess pointed and discharged in the antecubital fossa, but by the end of August the resultant sinus had ceased to discharge and had filled with granulation tissue.

Further Progress

In September the patient became ambulant and seemed to be making steady progress. His appetite, however, was capricious, and injections of vitamin-B complex were given. These had the effect of making the appetite almost voracious, and a high-protein diet, rather unpalatable to an average person, was consumed with ease. Diarrhoea developed at this time, with the passage of loose, pale, unformed, and very offensive stools. They resembled closely the stool of steatorrhoea. Dietary adjustment—namely, lowering of the fat content and administration of an ox-bile preparation—was followed by immediate improvement. His general condition was now so satisfactory that he was allowed home to continue convalescence. There was no jaundice, pallor had been replaced by good colour, and his weight was 9 st. 4 lb. (59 kg.), an increase of over 14 lb. (6.4 kg.) since the beginning of streptomycin treatment. The elbow-joint was immobilized in plaster, in the position of flexion to just less than a right-angle, and he was quite capable of dressing and eating, etc., with only one efficient arm.

Since discharge he has been seen regularly at fortnightly intervals. The gain in weight has been maintained and his appetite has been enormous. The sedimentation rate (Westergren) on November 15 was: first hour 17 mm., second hour 47 mm.; and on November 29, first hour 20 mm., second hour 47 mm. Stools were still rather pale and loose, and there was slight tenderness in the right umbilical region. Examination of the chest still showed no abnormality. The elbow-joint was gradually becoming ankylosed.

At the time of writing the patient feels well, but, while the degree of recovery following streptomycin is as yet very satisfactory, the ultimate prognosis must remain doubtful, with the possibility of recurrence to be considered.

I wish to express my thanks to Dr. D. K. Adams for permission to describe this case, which was treated in his wards, and to Mr. G. Dalziel, who performed the laparotomy. My thanks are also extended to Dr. Adams and Dr. W. Kyles for their guidance, help, and criticism during the preparation of this paper.

Medical Memorandum

Special Visits by Medical Officers of a Public Health Department

The visits of medical officers on the staff of a public health department to suspected cases of infectious disease receive but scant publicity. During serious epidemics this work becomes more obvious, but the regular visits which take place throughout the year are but little appreciated until an epidemic such as one of poliomyelitis throws them into relief.

An analysis of a miscellaneous list of such visits covering the period 1935 to 1950 for the City of Manchester is most revealing in showing the diagnostic difficulties that are most common. A miscellaneous list has been chosen to show the range of clinical acumen necessary in this special field. An analysis of these visits is presented in the accompanying table.

The screening of cases by public health medical officers becomes increasingly important, for the available accommodation in infectious disease hospitals is limited by shortages of nursing staff and a standstill in building extensions to these hospitals. This work is essentially clinical, and requires that those undertaking it shall have

Home Consultations by Medical Officers During 1935–50

Disease	Cases Referred	Cases Confirmed	Cases Not Confirmed	Examples of Revised Diagnosis by Consultant or Hospital
Diphtheria ..	21	6	15	Streptococcal septicaemia
Faucial includes pharyngeal	18	5	13	Tonsillitis, thrush, diphtheria carrier
Nasal ..	1	—	1	Faucial diphtheria
Laryngeal ..	2	1	1	Laryngitis
Carrier ..	—	—	—	
Erysipelas ..	13	7	6	Dermatitis, serum reaction, cellulitis
Enteric fever (typhoid or paratyphoid)	23	9	14	Henoch's purpura, malignant disease, tonsillitis, gastro-enteritis, cerebrospinal fever, colitis, infective endocarditis, anaemia, food-poisoning, and pyelitis
Cerebrospinal fever (meningococcal infection)	16	12	4	Acute purpura, rheumatic fever, neurasthenia
Measles ..	18	6	12	Erythema, rubella, enema rash, urticaria
Rubella ..	3	1	2	Urticaria, tonsillitis
Poliomyelitis (exclusive of 1947 outbreak, when 100 cases referred—51 not confirmed at home, 49 admitted to hospital; 16 cases not confirmed in hospital)	52	12	40	Neuritis, cervical adenitis, rheumatic fever, tonsillitis, pneumonia, subarachnoid haemorrhage, Bell's palsy, tuberculous meningitis, epilepsy, rheumatism, hysteria, cerebral thrombosis, febrile catarrh, pharyngitis, herpes zoster, arthritis, cerebrospinal fever, gastro-enteritis, otitis media, pyelitis
Scarlet fever ..	50	33	17	Rubella, tonsillitis, urticaria, sulphonamide rash, measles, exfoliative dermatitis, septicaemia
Smallpox (exclusive of 2 cases confirmed from outside city)	96	—	96	Folliculitis, dermatitis, varicella, erythema multiforme, urticaria, varicella and herpes, lichen urticaria, erythema, ecthyma, staphylococcal septicaemia, purpura, varicella and acne, measles, sulphonamide rash, iodide rash, furunculosis
Rash? infections	7	4*	3	Measles, rubella (3), serum reaction, urticaria, dermatitis
P.U.O.? infections	6	6*	—	Enteric fever, pneumonia, influenza, septic throat
Puerperal fever	6	5	1	Mastitis
Miscellaneous:				
Malaria ..	2	1	1	
Dysentery (bacillary)	1	—	1	Gastro-enteritis
Glandular fever	1	—	1	Nasal diphtheria
Syphilide ..	1	1	—	
Debility after Malta fever	1	1	—	
Epidemic parotitis	2	—	2	Tonsillitis, submaxillary adenitis
Pemphigus ..	2	2	—	
Encephalitis..	2	—	2	Rheumatism, scarlet fever
Typhus ..	1	—	1	Drug idiosyncrasy
Varicella ..	1	1	—	
Hemiplegia following influenza	1	—	1	Meningitis following otitis
Streptococcal infection	1	—	1	Agranulocytic angina
Influenzal pneumonia	1	—	1	
Total ..	328	107	221†	

* Diagnosis as in last column. † 199 home consultations, 22 hospital.

not only a sound background of knowledge gained in infectious disease hospitals but also many years of experience in the art of applying this knowledge. In this connexion the table shows the numerous pitfalls of diagnosis of poliomyelitis and the need for the public to be reassured by the comparatively few cases that are confirmed. The necessity for thorough screening of cases by experienced medical officers is essential if effective use is to be made of hospital beds.

This survey of consultations has not been made in any spirit of criticism. When one considers the list of revised diagnoses it is evident that in most cases the patient was suffering from a serious illness—in many instances requiring admission to hospital. It is intended to emphasize the need for team-work between the hospital, the medical practitioner, and the medical officer of health. There is still an important field of clinical work for the medical officer of health and a need to make the fullest use of the increasing accessory aids to diagnosis provided by the national Public Health Laboratory Service.

Reference to the table shows that only one case of bacillary dysentery was referred for home consultation and that comparatively few cases (21) of diphtheria needed a second opinion. The presumption is that in the case of diphtheria medical practitioners referred all suspicious cases to hospital; while in the case of bacillary dysentery they obtained bacteriological diagnosis and either treated the cases at home or sent them to hospital. There is a further possibility that some cases of dysentery were treated as gastro-enteritis.

Another interesting point is that there is an excellent confirmation rate for meningococcal infection (12 out of 16 cases) but confirmation rates for smallpox and poliomyelitis are low. A factor operating in these two serious diseases and responsible for the low confirmation rate is the anxiety of the medical practitioner not to miss the disease. The variety of revised diagnoses underlines this difficulty.

Over a period of 15 years, and exclusive of epidemics, as many cases of suspected poliomyelitis as of suspected scarlet fever were referred to the health department for a second opinion; this number represents one-sixth of the total cases. One might have expected a higher confirmation rate in diseases such as erysipelas, enteric fever, and measles.

Conclusions

A survey of 328 home consultations by medical officers of a health department over a period of 15 years has been made. These visits are exclusive of those carried out during major epidemics.

The diagnosed infection was not confirmed in 221 cases—199 after home consultation and 22 after admission to hospital. This represents very effective screening of cases and a considerable saving in hospital accommodation.

Examples are given of the variety of conditions which make the diagnosis of the specific infectious diseases a matter of considerable difficulty and call for the specialized training of medical officers of the public health service. The necessary team-work, with medical practitioners and laboratory and hospital services, leads to efficient administration in the control of infectious diseases in the community.

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N.A.P.T. has just published the 13th edition of the *Handbook of Tuberculosis Activities in Great Britain and the Commonwealth*. This is a complete directory of hospitals, sanatoria, clinics, regional hospital boards, hospital management committees, and tuberculosis services in the British Commonwealth, including addresses and telephone numbers. It is the first edition of the handbook to be published since the start of the Health Service, and therefore there is much new material presented.

Reviews

STARVATION

The Biology of Human Starvation. By Ancel Keys, Josef Brozek, Austin Henschel, Olaf Mickelsen, Henry Longstreet Taylor. With the assistance of E. Simonson, A. S. Skinner, and S. M. Wells. Volumes 1 and 2. Forewords by J. C. Drummond, R. M. Wilder, and C. G. King and R. R. Williams. (Pp. 1,385. $18.) Minneapolis: University of Minnesota Press. London: Geoffrey Cumberlege (Oxford University Press). 1950.

Some time in 1944, when the end of the war and the responsibilities of the victors were in sight, a little group of investigators at the University of Minnesota conceived the idea of making an experimental study of prolonged undernutrition and its relief by food. They argued that real knowledge about such matters was so scanty that their results could not fail to improve our knowledge of nutrition and to assist in the rehabilitation of the occupied territories. The idea was not altogether new, for Benedict and some collaborators had made a somewhat similar experiment in the closing years of the first world war. "L'idée c'est la graine,"* and although this little seed germinated with difficulty and without much official support, and for the last four years of its life had to subsist without any monetary manure at all, the authors have marketed a very fine plant.

The subjects of this ambitious experiment were 32 conscientious objectors. After a preliminary control period lasting for 12 weeks these 32 men were given a diet similar to those likely to be available in Europe, containing 50 g. of protein and 30 g. of fat and providing 1,570 calories a day. The investigators predicted that the men would lose about 25% of their body weights during the period of semi-starvation, which was planned to last 24 weeks, and this was a remarkably accurate prediction. For the rehabilitation period the men were split up into subgroups and the 1,570-calorie diet was supplemented to varying degrees by additional food. The supplements were too small at first and had to be increased, and the allowances of food during the rehabilitation period are a feature that perhaps may be criticized in this fine experiment. It is difficult to understand, for instance, why the investigators did not give one group an unrestricted calorie intake, but it is easy to be wise after the event.

The two large volumes which have now been published describing these experiments also include the most comprehensive review of the literature on undernutrition and starvation which has appeared up to the present time. The first volume contains three sections, each 180 to 240 pages in length, devoted respectively to the morphology, the biochemistry, and the physiology of starvation. The second volume opens with a section of similar length on psychology, and this is followed by the consideration of a number of special problems such as oedema, growth, and development, and the relationship of undernutrition to infectious diseases, particularly tuberculosis. A chapter is devoted to diabetes and another to neoplastic disease. The methods used, the detailed results of the authors' own investigation, and information about rations available during the second world war are relegated to appendices. Last, but not least, comes the impressive list of references. A rough calculation shows that there must be nearly if not quite 3,000 of these—with titles—enough surely for the most demanding seeker after knowledge.

The investigators satisfied themselves that the clinical syndrome they had under observation was dominated by a calorie deficiency. The diet provided all the vitamins necessary, and administering them did not accelerate rehabilitation. Nearly everyone with European experience after the recent war would certainly confirm this. The psychological side has very properly been given careful consideration and description, for the mental changes are some of the most subtle and also the most terrible likely to be met with in a starving community. Better to lose all the fat in the body than every sense of moral value! The historical part of this section is most interesting and might have been enormously enlarged.

For most people the hallmark of undernutrition is oedema, and Keys and his collaborators discuss its aetiology in considerable detail without coming to any definite conclusion. There are still plenty of problems in undernutrition for future investigators, but let us hope there are not many famines in which to investigate them.

Sir Jack Drummond has contributed a foreword, and the value of the book is aptly described in his concluding words: "This volume will soon take its place among the classic treatises on nutrition, a fitting reward for the years of thought and labour that Professor Ancel Keys and his 'band of brothers' gave to their formidable task."

R. A. McCANCE.

*M. Claude Bernard, *Introduction à l'Étude de la Médicine Expérimentale*, Paris, 1865.

BINOCULAR VISION

Researches in Binocular Vision. By Kenneth N. Ogle, Ph.D. (Pp. 345; illustrated. £1 17s. 6d.) Philadelphia and London: W. B. Saunders Company. 1950.

No book of first-class merit has appeared on binocular vision and space perception in English literature for many years, and it is well, in view of the completely new aspects of the subject opened up by the intensive study of aniseikonia by Ames and his co-workers at the Dartmouth Eye Institute in the U.S.A., that the whole subject should be reviewed and aligned with recent advances in knowledge. There may be some differences of opinion about the clinical importance of aniseikonia and the value of its optical correction, but there can be none about the marked influence exerted by a natural or artificially induced disparity in the size of the two retinal images on the physiological processes involved in the perception of space. Among the large staff of ophthalmologists, physicists, psychologists, and technicians who worked under the stimulus of Ames none is more qualified to review these researches than Kenneth N. Ogle. His presentation is perhaps somewhat mathematical for the average medical reader, but the writing is clear and the algebraic and geometric formulations are readily understandable and fundamentally simple.

He discusses a wide range of subjects—the horopter, Panum's fusional areas, cyclofusional movements, fixation disparity, magnification of images, prismatic distortion, depth clues, stereopsis, anomalous correspondence, asymmetric convergence, and ocular movements, to mention a few. Each proposition advanced is supported by well-defined and ably conceived experiments. The main theme advanced is the comparative precision and stability of the functional organization of corresponding retinal points, which are claimed to be an

innate property of the retinal elements, the directional value of which can be changed only by artificial means, as by the use of lenses or prisms. It will take much more research and time before the full potentialities of the methods of investigation employed are realized and all the questions raised can be adequately answered; but no better presentation of the basic principles of this difficult but absorbing subject can be found than in the present volume.

STEWART DUKE-ELDER.

PNEUMONIA IN CHILDHOOD

Pneumonie et Pneumopathies Aiguës de l'Enfant. Étude Clinique et Radiologique. By Professor Georges Mouriquand and Dr. Jacques Savoye. (Pp. 208; 90 figures. No price.) Paris: Vigot Frères. 1951.

For 40 years Professor Georges Mouriquand has studied pneumonia in childhood with special reference to the radiological appearances. With Dr. Jacques Savoye he has collected his experiences in this monograph. The earliest studies were actually made in 1905–6 with Professor Weill in Lyons, and are of historical interest, for there was at that time a "modest radiological apparatus" in the children's department of the hospital. Special interest was shown in a triangular shadow, usually in the right upper zone, and Professor Mouriquand has continued his contact with the subject, correlating this *x*-ray appearance with clinical signs and pathological findings.

This monograph does not presume to be completely comprehensive—for the subject would take considerably more space—but it is a remarkably interesting record of observations in a clinic where this common disorder of childhood has been carefully studied. The clinical discussion is particularly well done; that on treatment is curiously less good, but in this aspect differences in national practice come into the picture. All would agree with the dictum (in italics in the original) that children with pneumonia should above all drink and drink heartily, but drugs to reduce temperature given as suppositories must surely seldom be indicated. Throughout the monograph the problem of what the *x*-ray appearances mean in terms of pathology recurs in various forms, and in particular the value of radiology in differential diagnosis is well emphasized. This book is a typical French medical monograph and is welcome, as such works usually are.

ALAN MONCRIEFF.

PENICILLIN AND CARINAMIDE

Pharmacological Basis of Penicillin Therapy. By Karl H. Beyer, Ph.D., M.D., F.A.C.P. American Lecture Series. (Pp. 214; 37 figures. £1 12s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1950.

This interesting book contains an account of the factors affecting the use of penicillin, including the value of administration by all possible routes, the variation in concentration in the blood and in cerebrospinal and other fluids, and the incidence of toxic reactions. The evidence of Gale and his colleagues that penicillin acts by interfering with the uptake of glutamic acid and of lysine by certain Gram-positive organisms is given, and the author explains that if these organisms become penicillin-resistant they lose their ability to assimilate glutamic acid, and then become Gram-negative.

The main feature of the book is the account of the introduction of carinamide, for which the author is responsible, as a substance capable of interfering with the excretion of penicillin by the renal tubules. By this means the concentration of penicillin in the blood is maintained at a much higher level than otherwise, with an increased therapeutic effect. Dr. Beyer regards the excretion of penicillin by the renal tubules as being an enzymatic process, which can be inhibited by a neutral substance allied in structure to penicillin, just as the oxidation of tyramine by amine oxidase can be inhibited by indolethylamine. His search for the harmless substance and discovery of it in carinamide (4'-carboxyphenylmethane sulphonanilide) must be regarded as a brilliant achievement in medical research. It is interesting to note that much of the work of finding a suitable agent was done by the aid of slices of frog kidney in which the excretion of phenol red into the lumen of the tubules can be seen by naked eye, and the inhibition of this excretion can be studied. It is a pleasure to note that the author has given full attention to work outside his own country.

J. H. BURN.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Elements of Bacterial Cytology. By Professor G. Knaysi. 2nd ed. (Pp. 375. 40s.) London: Constable. 1951.

The Shadow of the Gallows. By Viscount Templewood, D.C.L., LL.D., Litt.D. (Pp. 159. 8s. 6d.) London: Victor Gollancz. 1951.

Public Health is People. By E. L. Ginsburg. (Pp. 241. 14s.) London: Geoffrey Cumberlege. 1950.

Scientific Thought in the Twentieth Century. Edited by A. E. Heath, M.A. (Pp. 387. 42s.) London: Watts. 1951.

Incontinence in Old People. By J. C. Brocklehurst, M.D. (Pp. 191. 30s.) Edinburgh: E. and S. Livingstone. 1951.

The Teaching of Parentcraft. By L. G. Housden, O.B.E., M.D. (Pp. 140. 7s. 6d.) London: Methuen. 1951.

Microdiffusion Analysis and Volumetric Error. By E. J. Conway, M.B., D.Sc., F.R.S. 3rd revised ed. (Pp. 391. 25s.) London: Crosby Lockwood. 1950.

Louis Pasteur: Free Lance of Science. By Dr. R. J. Dubos. (Pp. 418. 18s.) London: Victor Gollancz. 1951.

Milk: Production and Control. By W. C. Harvey, M.D., D.P.H., F.R.San.I., and H. Hill, F.R.San.I., A.M.I.S.E., F.S.I.A. 3rd ed. (Pp. 758. 57s. 6d.) London: H. K. Lewis. 1951.

Cancer As I See It. By H. W. Abelmann, M.D. (Pp. 100. $2.75.) New York: Philosophical Library. 1951.

Progressive Resistance Exercise. By T. L. DeLorme, B.S., M.D., and A. L. Watkins, A.B., M.D. (Pp. 245. $5.) New York: Appleton-Century-Crofts. 1951.

Pioneer Doctor. By L. J. Moorman, M.D. (Pp. 252. $3.75.) Norman, Oklahoma: University of Oklahoma Press. 1951.

Gesichts-Gymnastik. By Dr. R. Drobil. (Pp. 85. M. 10.) Vienna: Wilhelm Maudrich. 1951.

Reports from the Institute of Social Medicine. (In Bulgarian.) Vol. 2. (Pp. 381. No price.) Sofia. 1950.

Die Entzündungsbestrahlung. By Dr. R. Glauner. 2nd ed. (Pp. 189. M. 18.60.) Stuttgart: Georg Thieme. 1951.

Leitfaden der Blutmorphologie. By L. Schudel. 7th ed. (Pp. 51. M. 14.80.) Stuttgart: Georg Thieme. 1951.

Lehrbuch der Rontgendiagnostik. By H. R. Schinz and others. Vol. 3 (The Skeleton). 5th ed. (Pp. 1,406. M. 82.) Stuttgart: Georg Thieme. 1951

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SKIN HOMOGRAFTS

In 1947 the Swiss father of 6-year-old twin sons Victor and Pierre became aware of a third child, Eric, whose appearance was so astonishingly like Victor's that they might almost have been identical twins. When Eric proved to have been born in the same clinic and on the same night as the other two, it seemed quite possible that the children had been muddled up and allotted to the wrong parents. Identical twins are usually recognized to be such by a systematic point-for-point comparison of their physical characters. A comparison supervised by Professor Franceschetti[1] made it fairly certain that Victor and Eric were indeed identical twins, for in addition to their general similarity they had certain minor but rare physical abnormalities in common; and detailed blood grouping showed that Pierre could not have been the son of his alleged mother, although Eric could have been his alleged mother's son. The test eventually agreed to be conclusive was this: small skin grafts were exchanged between Victor and Eric, and these survived and behaved like ordinary "autografts" of skin—i.e., like skin transplanted from one part to another of the same person. On the other hand, grafts exchanged between Victor and Pierre quickly became necrotic. The grafting test, designed and carried out by Sir Archibald McIndoe,[2] proved that Eric and Victor were identical twins. It did not exclude the possibility that Victor and Pierre were ordinary twins or brothers, but the blood-grouping test had done that much beforehand. The confusion was then sorted out, and the story ended happily.

The principle made use of in this test is now well understood. Skin grafts cannot be transplanted with permanent success between human beings of ordinary genetic disparity—which means, in effect, between other than identical twins. For permanent grafting the plastic surgeon is therefore obliged to cover a skin defect by using skin taken from elsewhere on his patient's body. The skin used for grafting is either cut so thin that its donor area can heal within a week or two by the upgrowth of epithelium from the truncated hair follicles; or, if the graft is thick, its donor area is resurfaced by a thin graft cut from elsewhere. The use of identical twins as skin donors cannot but be rare, since only one patient in about 350 can be expected to have such a twin; but it has once happened. A young French soldier with severe and extensive phosphorus burns of his legs was alleged to have been seen walking round the hospital in splendid health shortly after a preliminary autografting operation. It was his identical twin who had been seen, and his skin was used by Converse and Duchet[3] to complete his brother's grafting operation with complete and permanent success. Cattle, it should be said, are more privileged or less exacting than human beings, for skin can be exchanged with permanent success between *non*-identical cattle twins, even when they are of different sex.[4] This anomalous tolerance to each other's tissue is the consequence of their normally having a confluent foetal blood supply, which incidentally gives them identical blood groups as well.[5]

Tissue transplanted from one individual to another of the same species is said to constitute a "homograft." Skin homografts are by no means altogether useless; they are quite widely employed for temporary repair (particularly of badly burnt children) in the full recognition of their being destroyed within about a month of transplantation and quite often sooner. Their purpose is to tide the enfeebled patient over the dangerous period that follows extensive skin loss, on the principle that the best dressing for an area of skin loss is skin itself. (Not everyone believes that skin homografts always fail, but this is due to an understandable confusion between the survival of living foreign cells and the endurance of the more resistant fibrous skeleton of the corium of the graft. The corium may sometimes be overgrown by the patient's own epithelium and infiltrated anew by his blood vessels in such a way as to give a fairly lifelike imitation of a truly surviving graft.)

A method of treatment that made possible the prolonged or indefinite survival of skin transplanted from one person to another might obviously be of considerable clinical value, particularly in wartime.

1 Franceschetti, A., Bamatter, F., and Klein, D., *Bull. schweiz. Akad. med. Wiss.*, 1948, **4**, 433.
2 McIndoe, A., and Franceschetti, A., *Brit. J. plast. Surg.*, 1950, **2**, 283.
3 *Plast. reconstr. Surg.*, 1947, **2**, 342.
4 Work cited by Billingham, Krohn, and Medawar in this issue.
5 Owen, R. D., *Science*, 1945, **102**, 400.
6 *J. Amer. med. Ass.*, 1951, **145**, 85.
7 *Plast. reconstr. Surg.*, 1951, **7**, 85.
8 Webster, J. P., *Ann. Surg.*, 1944, **120**, 431; Strumia, M. M., and Hodge, C. C., ibid., 1945, **121**, 860.
9 *J. Anat., Lond.*, 1943, **77**, 299.
10 Ibid., 1944, **78**, 176; 1945, **79**, 157; *Brit. J. exp. Path.*, 1946, **27**, 9, 15; 1948, **29**, 58.
11 *Brit. J. exp. Path.*, 1950, **31**, 670.
12 Craddock, C. G., and Lawrence, J. S., *J. Immunol.*, 1948, **60**, 241.
13 *Quart. J. micr. Sci.*, 1948, **89**, 239.
14 *J. Path. Bact.*, 1942, **54**, 51.
15 *Brit. J. exp. Path.*, 1950, **31**, 306.
16 *Cancer Res.*, 1947, **7**, 634.

Visitors to the National Research Council's recent symposium on burns at Washington will have heard favourable, if inconclusive, reports on the use of A.C.T.H. for such a purpose, and M. J. Whitelaw has lately published a suggestive case history.[6] Subsequent discussion of the value of A.C.T.H. has been critical in tone, and the life of a homograft transplanted to a patient described by Baxter, Schiller, and Whiteside[7] was not prolonged by its administration. Billingham, Krohn, and Medawar, writing in this issue, have now shown that the administration of cortisone in 10 mg. daily doses prolongs the life of skin homografts in rabbits by a factor of three or four. By deliberately choosing to exchange skin between rabbits of wide genetic disparity they made the test particularly exacting. Skin homografts transplanted to untreated rabbits survived about a week before the last of the transplanted cells was finally destroyed, but those grafted to cortisone-treated rabbits lasted three or four weeks or even longer. The administration of cortisone was not without secondary surgical disadvantages. The primary healing of the grafts was somewhat impaired; but in the human being, in whom the reaction against foreign skin is slower of progress, they believe that this could be got round by giving the grafts a few days to heal soundly before the administration of cortisone began. Cortisone treatment did not significantly prolong the life of homografts on rabbits that had already been immunized by an earlier grafting of skin from the same donor, and the authors therefore argue that cortisone inhibits the systemic development of the immune state rather than its local fulfilment in the graft. But, whatever its mechanism may be, cortisone does indeed greatly prolong the life of homografts in rabbits. Whether it will do as much for the human being has yet to be seen. It should be added that the clinical use of skin homografts does not depend upon a donor's presenting himself when an emergency arises, for skin can for many weeks be stored alive, or in "suspended animation," by methods hardly more elaborate than putting it into an ordinary refrigerator.[8]

What is the mechanism by which, in the ordinary course of events, skin homografts are inevitably destroyed? Gibson and Medawar[9] and Medawar[10] have shown that homografts are not set upon at once; they behave at first in a manner indistinguishable from that of autografts. Thereafter their survival time depends upon the quantity of skin that has been grafted—the more that is grafted, the shorter the time it lives—and, of course, upon the genetical relationship between the donor and the recipient. The life of homografts transplanted to a recipient that has already reacted against homografts from the same donor is very much curtailed. For these and other reasons it has been argued that resistance to foreign skin depends upon an actively acquired immunity similar in broad outline to that provoked by more remotely foreign cells like bacteria. This general interpretation has been supported by the recent work of Dempster, Lennox, and Boag,[11] who find that the *x*-irradiation of rabbits prolongs the life of skin homografts—i.e., weakens the immunity reaction they provoke—in a manner closely analogous to its depression of the classical antibody response.[12] Antibodies to skin homografts have nevertheless not yet been revealed by reactions *in vitro*. Medawar[13] found that skin explants from a donor rabbit could be cultivated with complete success in a medium composed of serum and tissue extracts from a highly immunized recipient, even when the explants were glued by means of clotted plasma to, for example, lymphoid tissue from the recipient. Tests *in vivo* have given more positive results; protective antibodies were shown by Gorer[14] to be formed in response to grafts of leukaemic cells in mice, and Woodruff and Forman[15] have lately shown that serum from rats immunized by skin homografts caused a transient lymphopenia when injected into their respective donors—a result that might have been due to the formation of iso-antibodies, because leucocytes and skin epithelium are known to share antigens in common. It is possible that the subtle *in vitro* tests that have been developed since the discovery of incomplete and conglutinating antibodies will help to reveal the mechanism of immunity to transplanted skin. Gorer, who has long maintained that immunity to tumour homografts is essentially similar to that provoked by normal tissues, has demonstrated an overlap between the antigens of red cells and of transplanted tumours in mice,[16] and has been able to reveal the former not only by classical agglutination methods but also, more sensitively, by the conglutination test. Much still remains to be done, however, to translate tissue immunity from the biological to the test-tube level of analysis. The whole problem is a challenge to the ingenuity of biologists and clinicians—not only as it relates to skin, cartilage, nerve, and bone, but to the ductless glands as well, in which purely endocrinological influences (such as those embodied in Halsted's Law) are superimposed upon and may greatly modify the ordinary immunological response. Whether it is useful, proper, or expedient to re-equip one human being with tissue derived from another is a question that admits of no general answer; but that it will one day be *possible* can now hardly be in doubt.

MALIGNANT DISEASE OF THE THYROID GLAND

Two studies of malignant disease of the thyroid gland have recently been published. Roualle[1] has examined the records of 100 consecutive cases seen at St. Bartholomew's and its sector hospitals between 1931 and 1948, and Hare and Salzman,[2] of the Lahey Clinic, have followed 198 cases diagnosed before 1936. Thyroid malignancy is rare outside endemic goitre regions, accounting for some 300 deaths annually in England and Wales, compared with nearly 8,000 deaths from mammary carcinoma. It is therefore unusual for any one surgeon to assemble a sufficiently large personal series to enable him to build a picture of the disease in all its aspects. In general there is close agreement between the British and American experience, although allowances have to be made for differences in composition of the two series and in the methods of recording employed. Thus women are three times as numerous as men in the British series and six times as numerous in the American series. In the British series 53% of patients were known to have had thyroid swellings from 2 to more than 20 years before operation—malignancy having apparently developed *de novo* in the remainder—whereas the malignant growth is described as having arisen in a pre-existing tumour in every American case. Roualle classified his patients according to clinical as well as pathological findings, the essential clinical factor being the presence or absence of clinical suspicion of malignancy before operation. As in other series, the best results were obtained in cases in which malignancy was unexpectedly revealed by histological examination of an apparently localized and benign adenoma. Fifteen per cent. of Roualle's patients were of this type, and in a further 24% complete excision was possible in spite of pre-operative suspicion of malignancy on clinical grounds. These considerations are unfortunately omitted from the American report, though it seems that all the cases were operable, and malignancy was unsuspected in every case of "adenoma with invasion" (49 cases) and in an unstated number of other types. In Roualle's series 30 cases were inoperable, either on surgical grounds or because of the presence of distant metastases. The American series contained a higher proportion of the more slowly growing papillary growths. Since Roualle's series includes cases operated on as late as 1948, he does not attempt to record 20-year survivals. When all these factors are taken into account it is not surprising that the American results include a higher proportion of long survivals: there were 5% of 20-year survivals and 14%, 40%, and 57% respectively of 15-, 10-, and 5-year survivals. In the smaller British series 33% survived for 10 years or more and 52% for 5 years.

The prognosis of thyroid carcinoma varies with pathological findings. Undifferentiated growths, which often arise in long-standing tumours in elderly women and were often mistaken for sarcomas in the past, are by common consent the most malignant. They infiltrate extensively and metastasize widely, respond poorly to radiotherapy, or else recur rapidly. Nevertheless 8 of 39 cases in the American series survived 5 years, 3 of them 10 years. Papillary growths, which are found more often in younger patients, often grow slowly and form metastases late in local lymph-nodes, where they were formerly regarded as "lateral aberrant thyroids." They are radio-sensitive, and survival figures are good: in both series 80% of these cases survived 5 years, and 60% survived 10 years, and out of 86 cases in the American series 23% and 7% survived 15 and 20 years respectively. Alveolar growths, which tend to invade small veins, give rise to blood-borne metastases more readily, sometimes while still confined within the capsule and arousing no suspicion of malignancy (Cohnheim's "benign metastasizing goitre"). In both series 60% of these cases survived 5 years, and rather more than half of these survivors were alive after 10 years. Even the presence of regional and distant metastases is often compatible with survival for many years.

The origin of so many thyroid carcinomas in pre-existing tumours raises the all-important question of when to excise apparently innocent nodules as a prophylactic measure. As Roualle points out, excision of every goitre in this country would necessitate several hundred thousand operations, as a result of which just over half of the 300 annual deaths from malignant thyroid growths would be averted. Clearly some kind of selection is necessary, and there is general agreement that it is the solitary nodule, especially in young persons, which should be regarded as dangerous. Hare and Salzman found that 10% of single thyroid nodules operated upon were malignant, which they believe justifies excision of all single tumours, a conclusion also reached by Roualle and by Branson and Houston,[3] who add that "it may require a good deal of moral courage on the part of the general practitioner to persuade a patient with a small nodule in the thyroid gland, which may have been present for many months without causing symptoms, to submit to operation." Most surgeons would agree with this view, and in these days of improved operative and anaesthetic technique fewer patients may be expected to decline the offer of having a potentially dangerous thyroid nodule removed.

[1] *Ann. roy. Coll. Surg. Engl.*, 1950, **7**, 67.
[2] *Amer. J. Roentgenol*, 1950, **63**, 881.
[3] *Lancet*, 1949, **2**, 979.

ANTIBODIES AND THE FOETUS

For more than half a century arguments have raged over the method by which the baby develops its immunity. Elsewhere in this issue Dr. H. J. Parish describes much of the recent work on the transmission of antibodies. Originally these were thought to be too large to pass the undamaged placenta, but in 1907, from the results of animal experiments, Lochead[1] was able to deny this and postulate some secretory mechanism dependent upon living cells. Nevertheless for many years afterwards a theory of simple filtration held sway, and it is not surprising that this mechanism was related to the number of cell layers which separate maternal and foetal blood, thanks to the comparative studies of Grosser[2] and, much later, Mossman.[3,4] Recently, however, the passage of antibodies across the placenta has been carefully studied, and the theory of filtration is once more open to doubt. Among the many puzzling facts not explained by simple filtration are findings of antibody concentrations in the newborn greater than those in the mother.[5-7] These observations fit well with the high values for gamma globulin in the serum of newborn babies.[8] The filtration conception fails also to account for the selection observed by Timmerman,[9] who found that typhoid H agglutinins reached the baby during pregnancy, whereas O did not. It was a significant finding, too, that in colostrum O agglutinins were of higher titre than H.

At the same time the view that transmission of antibodies is a vital process akin to secretion is upheld by the most recent work on animals. Using delightfully ingenious techniques in a series of experiments in rabbits, Brambell and his colleagues[10-12] have carefully traced the route taken by antibodies. They have proved conclusively that antibodies pass from the maternal blood stream into the uterine cavity and through the yolk-sac splanchnopleure into the vitelline vessels of the embryo rabbit. They have further shown that not only is the placenta impermeable to antibodies and so is bypassed, but that antibodies reach the foetal circulation before the placenta is even formed. This work from Bangor casts the very greatest doubts upon any filtration mechanism, since it makes clear that the simplest placenta of all, that of the rabbit—where only one cell layer separates maternal from foetal blood—is impermeable to antibodies. Caution is of course necessary in translating these results in terms of humans, for, as Brambell points out, the yolk sac could not serve as a route in man as it does in rabbits. In their latest communication to the Royal Society, Brambell and his colleagues show that antibodies could be detected in the amniotic fluid and foetal stomachs when the doe rabbit had received injections of immune serum. It is interesting that the foetal rabbit stomachs concentrated the antibodies very greatly, but, oddly enough, no absorption into the foetal circulation from the stomach occurred.

While it is idle to speculate on the actual route taken by antibodies in man, the possibility remains that absorption through the stomach may take place: perhaps we drink our early immunity *in utero*, just as the ungulates do theirs after birth. There is, on the other hand, the theory that the human baby makes its own antibodies from "altered" amino-acid groupings provided by the mother.[13] Both these conceptions would account for the known facts.

1 *Trans. Edinb. obstet. Soc.*, 1907, **33**, 120.
2 *Vergleichende anatomie und Entwicklungsgeschichte der Eihaute und der Placenta mit besonderer Berucksichtigung des Menschen*, 1909, Vienna.
3 *Amer. J. Anat.*, 1926, **37**, 433.
4 *Contr. Embryol. Carneg. Instn*, 1937, **26**, 129.
5 Barr, M., Glenny, A. T., and Randall, K. J., *Lancet*, 1949, **2**, 324.
6 Murray, J., Calman, R. M., and Lepine, A., ibid., 1950, **2**, 14.
7 Bryce, L. M., and Burnet, F. M., *J. Path. Bact.*, 1932, **35**, 183.
8 Longsworth, L. G., Curtis, R. M., and Pembroke, R. H., jun., *J. clin. Invest.*, 1945, **24**, 46.
9 *Z. ImmunForsch.*, 1931, **70**, 388.
10 *Proc. roy. Soc. B*, 1948, **135**, 390.
11 Ibid., 1949, **136**, 131.
12 Ibid., 1950, **137**, 239.
13 Calman, R. M., and Murray, J., *Endeavour*, 1951, **10**, 27.

METRIC SYSTEM IN MEDICINE

The Committee on Weights and Measures Legislation, whose report has recently been published,[1] has wisely recommended that weights and measures in medicine and pharmacy should be given entirely in the metric system. The much simpler calculations that the metric system allows have long made this change desirable; the urgent necessity for it is obvious now that so many remedies are synthetic chemical products marketed in doses measured in the metric system. The absurd anomaly of having to prescribe in two different systems of measurements taxes the physician's memory, and the use of easily mistaken hieroglyphics in the apothecaries' system has its dangers, as a medico-legal case reported this week at page 1210 shows. For some time now this *Journal* has given the metric equivalents of other measurements.

The Pharmaceutical Society in its evidence to the committee pointed out that its members must work in three systems—the avoirdupois, the metric, and the apothecaries'. It considered that some simplification is necessary in the interests of human life and welfare because of the present inconvenience and possibility of confusion. For many years the Society and the British Pharmacopoeia Commission have advocated that the medical and pharmaceutical professions should work in the metric system only. Evidence submitted by the B.M.A. stated that the medical profession is probably in favour of using the metric system, but that so far as prescribing is concerned abolition of the use of the apothecaries' system would cause what would almost amount to hardship to the middle and older generations of doctors. This objection seems to be met by the committee's recommendation that there should be a transition period of five years. The committee thought that a longer time, such as 20 years, would merely spread out the period of inconvenience, and that the medical and pharmaceutical professions should be able to surmount the difficulties satisfactorily and far more quickly by the combined efforts of all their members.

The report therefore recommends that the Government should invite the medical and pharmaceutical professions to collaborate in the adoption of the metric system at the end of the five years and that the Government should use its own direct influence to

1 *Report of the Committee on Weights and Measures Legislation.* (Board of Trade.) London: H.M.S.O.

"achieve this sensible and worthwhile goal." In conjunction with these arrangements the apothecaries' units used in medicine would cease to be lawful at the end of the five-year period, and the hieroglyphic symbols would no longer be recognized as lawful abbreviations.

Discussing the whole field of weights and measures, the committee wishes to see the imperial system eventually replaced by the metric and advocates a decimal coinage. It recognizes that the abolition of the imperial system is "contentious in the extreme" and is aware of "the element of human inertia." The medical profession would surely be failing in its duty if it gave way to inertia. There is probably little danger of that, for the laboratories where the new synthetic drugs are prepared necessarily work in the metric system and must impart some momentum to our profession. But more than passive acquiescence is needed in view of this committee's report, and it is to be hoped that the medical profession will study its recommendations and investigate how they may soon be fulfilled. It is not often that a Government report is as courageous as this one, and rarely so contentious. The committee is to be congratulated on recommending a thoroughly sound scheme.

A DANGER OF THE NEWER ANTIBIOTICS

The Council on Pharmacy and Chemistry of the American Medical Association is now requiring[1] a warning statement to be added to the label of bottles of aureomycin, chloramphenicol, and terramycin, pointing out that when susceptible bacteria are suppressed by these drugs *Monilia* (*Candida*) and other yeast-like organisms may appear. It is well recognized that these antibiotics, and also penicillin if given in large doses or applied locally, may transform the flora of the mouth, with or without resulting symptoms. *Candida albicans* is highly resistant to all antibiotics in use as chemotherapeutic agents, and is one of the organisms which survive and multiply in the mouth when they are administered: the development of frank thrush has sometimes been observed. Since the newer antibiotics, unlike penicillin, also affect the flora of the lower bowel, the same or similar organisms have been found in markedly increased numbers in the faeces, although there seems to be no evidence that they cause any lesion in the bowel. Thus, so far as the alimentary tract is concerned, this is a well-known effect and not one which need usually cause any serious alarm, although a severe stomatitis may occasionally call for interruption of treatment.

It appears, however, that other parts of the body may become involved, since the statement continues: ". . . If this replacement occurs in a lung abscess, bronchiectatic cavity or in certain other lesions, a condition is created which may be unfavourable for the patient. Deaths from pulmonary moniliasis following therapy with the new antibiotics are known. Also instances of cutaneous moniliasis mistaken for sensitivity have been noted when the newer antibiotics were used in the treatment of disease." Presumably this statement will not necessarily appear on packages of these drugs manufactured in Britain, and the profession may therefore like to know that it has been thought necessary to issue such a warning in the U.S.A. The much more extensive use of these drugs generally in America has evidently brought to light complications with which we are still unfamiliar. Skin infections with *Candida* (*Monilia*) need cause confusion only if they imitate reactions of hypersensitivity, but pulmonary moniliasis is a much more serious matter, and it would be interesting to know in what circumstances it has been seen to develop and what evidence there is that it has actually caused death. Although it is not uncommon to find *Candida* in sputum—and demonstrable bronchial lesions may occasionally be caused by it—infection of the lung itself is very rare, and usually secondary to some other condition such as tuberculosis or new growth.

[1] *J. Amer. med. Ass.*, 1951, **145**, 1267.

PUBLIC HEALTH SALARIES

The Industrial Court has now given its award on the matters referred back to it for decision, and the results will probably cause satisfaction in the public health service. A report of the award appears at page 209 of the *Supplement*. After the Court gave its first award[1] it referred back certain matters for negotiation between the staff and management sides of Whitley Committee C (public health). These were the terms and salaries of deputy medical officers of health, divisional or area medical officers, and medical officers holding mixed appointments. The two sides of the Whitley Committee failed to agree, and they therefore invoked the aid of the Industrial Court for decision.

The most important feature of the award is that medical men and women in the public health service will be paid in accordance with scales that are designed specifically for them, and not on scales linked with those on which laymen are paid. The management side wanted a system of grading introduced which derived from salary scales paid to lay officials employed by local authorities. The staff side contended that the local authorities' proposals would lead to "subjective" judgment on what doctors should be paid, that they were not designed specifically for medical officers, and that they would not fit into the framework established by the main award.

The Court agreed that the salaries of deputy medical officers should be linked to those of the doctors for whom they deputized—namely, medical officers of health—and awarded a starting salary which is 66⅔% of the minimum scale adopted by the employing authority for the post of medical officer of health, with annual increments equivalent to those of the M.O.H. Divisional or area medical officers have their own scale of salaries rising from £1,250 a year by annual increments of £50 to £1,650, with additions ranging from £50 upwards to be paid in accordance with the population of the division. Medical officers with mixed appointments are to receive for their salary relating

[1] *British Medical Journal Supplement*, 1950, **2**, 255.

to county council work the appropriate proportion (calculated in accordance with the Spens formula for consultants) of their salary as assistant medical officers, or divisional or area medical officers, as the case may be, plus the appropriate proportion of the salary fixed for county district medical officers of health under the previous award and a similar proportion of £100.

The case presented to the Industrial Court has been a long and intricate one, and the medical officers' representatives have argued it compellingly. Much praise is due to them for the success that has attended their work. These awards should constitute a charter—open to revision by negotiation through Whitley machinery—for medical officers in the public health service, and ensure that their unique place in the country's public services is rewarded by scales of pay specifically designed for them.

SOCIAL MEDICINE

For better or for worse the universities—or at least many of them—are now committed to social medicine. It is too early to attempt an objective assessment of what has been achieved, and the thoughtful observer may still be in two minds about whether discussion of recent advances in social medicine is to be regarded as encouraging evidence of progress or as an example of whistling to keep up one's spirits. Yet time passes quickly, and the publication of *A Report on the Work of the Institute of Social Medicine, Oxford, 1943–50*, as well as the sixth annual report (for the year 1950), comes as a reminder that it is over seven years since the late Professor J. A. Ryle left the Regius Chair of Physic at Cambridge to become the first head of the first department. Academic social medicine, in the sense in which it is understood in Great Britain, started in Oxford. It did not end there. Nevertheless there are two reasons why the achievement of the Oxford school could not fail to have a special significance: the first was the fact, surprising enough, that this promising if hazardous adventure was launched by the most ancient of our universities; the second was the unusual distinction as a clinician of its first chief.

As a site for social medicine Oxford would not have been everyone's first choice; indeed, from the point of view of the research worker its only conspicuous assets were the Bodleian and the Morris works. Perhaps it is easier for old institutions to take the patient view that new enterprises should be approached on the principle that the 80% which is error is worth tolerating for the 20% which is sense. As to teaching, there were also difficulties, for the number of students doing clinical training was small. In any case it was evident from the beginning that the Institute would be judged mainly by its achievement in research.

It is not easy to assess the merits of the numerous papers which have appeared from the department during the seven years of its existence. Nor would it be reasonable after doing so to pass judgment on the Institute, much less on social medicine. For if the evidence at this point seems inconclusive it should be remembered that it is also incomplete. Few professors who have had the experience of starting a new department in a medical faculty would doubt that it takes at least five years to get under way—to find facilities, money, and (most important of all) suitable staff. The professor of social medicine is confronted with yet another difficulty peculiar to his subject. His research depends very largely on local opportunities for field inquiry, and, unlike his colleague in the laboratory who may bring with him his animals and his unfinished papers, he must find new problems or adapt old problems to new opportunities.

To-day there are many departments of social medicine, and in time no doubt they will write many papers. Inevitably some will be bad papers; yet if even a few of them introduce to medical research methods which are both novel and fruitful the game will most decidedly have been worth the candle. The alchemists did not transmute base metal into gold, but in attempting to do so they launched the science of chemistry. The day may come when it will occasion less surprise to recall that a man left a regius chair of medicine to become the first head of the first department.

THE HASTINGS MEMORIAL FESTIVAL

Doctors visiting Worcester on Wednesday, May 30, for the Sir Charles Hastings Memorial Festival will enjoy an interesting occasion and receive a cordial welcome from members of the Worcester and Bromsgrove Division of the B.M.A. Hospitality in Worcester on the Tuesday or Wednesday night is offered, and any doctor who would like to accept it should write without delay to Dr. C. Mackie, The Lower House, Stourport. The celebrations honouring the founder of the B.M.A. will begin with a memorial service in the cathedral, to be conducted by the Bishop of Worcester. Lunch follows (tickets 1 guinea, from Dr. M. P. Martin, 109, Laugherne Road, Worcester), and then Dr. W. H. McMenemey will deliver the first Sir Charles Hastings Memorial Lecture at 3 p.m. Tea will be provided, and some relics of Sir Charles Hastings will be on view at the Worcester Royal Infirmary. The full programme appeared in the *Supplement* of May 19 (p. 207). The festival promises to be a fitting celebration of the work of a most unusual man. Spending his whole working life in the provinces at a time when the capital cities exerted a much stronger attraction on men of outstanding ability than they do to-day, Hastings came both to excel in the practice of medicine and to display great administrative gifts. The organizers of this festival are hoping for a large attendance; the occasion is worthy of it.

The Festival Scientific Meeting, jointly organized by the Royal Society of Medicine and the B.M.A., will be opened on June 4 at the Barnes Hall, Royal Society of Medicine, 1, Wimpole Street, London, W.1. The opening ceremony will be performed at 2 p.m. by the Rt. Hon. the Earl of Athlone, K.G., Chancellor of the University of London, accompanied by H.R.H. the Princess Alice, G.C.V.O., Chancellor of the University College of West Indies.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

INFECTIVE HEPATITIS

BY

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It is now generally accepted that infective hepatitis is an infectious disease due to a virus. The condition designated "catarrhal jaundice" since the time when Virchow described a plug of mucus obstructing the lower end of the common bile duct in a fatal case is now recognized as being identical with infective hepatitis. Biopsy and necropsy studies, in many cases conforming exactly to the clinical picture of catarrhal jaundice, have shown without doubt that the underlying lesion is a hepatitis with necrosis of liver cells, especially in the centrilobular zones, disruption of the liver cell columns, and considerable cellular infiltration mainly in the portal tracts.

A closely related disease, apparently identical in its clinical and pathological manifestations, is known to follow the injection of blood or serum from certain donors. This condition, known as homologous serum jaundice, has a longer incubation period than ordinary infective hepatitis—50–140 days compared with 25–36 days—and often has a more severe clinical course and a somewhat worse prognosis.

Epidemiology

In civilian practice large epidemics are rare, though apparently isolated cases and small epidemics are by no means uncommon. Conditions in war, however, especially among the armed Forces, seem to provide ideal conditions for epidemic spread, and in both the recent world wars epidemics of crippling proportions occurred, particularly in the Mediterranean theatres.

Extensive epidemiological studies have suggested two possible routes of infection—by droplet inhalation from infected pharyngeal secretions, or by ingestion of contaminated food or water. The ability to transmit the disease to human volunteers by spraying the throat with nasopharyngeal washings provides confirmatory evidence for droplet infection. On the other hand F. O. MacCallum found in some cases that nasopharyngeal washings were not infectious, but he succeeded in transmitting the disease with faeces given in capsules. These observations suggest that transmission by ingestion of faecal contaminated material is a distinct possibility, since the virus is shown to be present in faeces. The discordant results of different epidemiologists may perhaps be explained by strain variations in different epidemics, some being excreted into the nasopharyngeal secretions and giving rise to droplet infections, while in others excretion is mainly via the faeces, transmission in such epidemics being mainly by ingestion. For adequate epidemic control both routes of infection should be anticipated and prevented so far as is possible.

Owing to the minute quantity of blood or serum that may convey homologous serum jaundice, the most stringent aseptic precautions must be taken to prevent large outbreaks of this type of hepatitis. The use of one syringe and a different needle for each subject in a series of mass injections of any kind has been shown to be inadequate to prevent cross-infection. The only sure technique in such cases is to provide a heat-sterilized needle and syringe for each subject. Owing to the great increase in the number of blood and plasma transfusions, cases of homologous serum jaundice must be expected to arise fairly often until some satisfactory means of sterilizing the blood and plasma is developed; ultraviolet irradiation has unfortunately been found unreliable.

Symptomatology

It is convenient to consider the clinical manifestations in two stages determined by the appearance of jaundice.

Pre-icteric Stage

In almost every case the appearance of jaundice is preceded by a prodromal phase characterized by gastrointestinal symptoms, particularly nausea and loss of appetite. Fever is often present with its usual accompaniments of headache, malaise, and some general aches and pains. It is rarely severe, though in some cases it dominates the prodromal picture. In most cases the temperature falls with the appearance of jaundice some one to six days after the onset of symptoms. In some cases, however, fever persists for a few days with the jaundice. In a small proportion of cases a period of several days of normal temperature and comparative well-being may intervene between the prodrome and the appearance of jaundice, which in these cases is usually accompanied by a recurrence of the fever for a few days.

The most characteristic and suggestive features at this stage are upper abdominal pain, usually on the right side, and loss of appetite associated with nausea. Vomiting and diarrhoea also occur in about one-fifth of the cases and may result in dehydration. Physical signs are not very helpful. The liver may be enlarged and tender and the spleen just palpable, but the incidence of splenomegaly varies considerably in different epidemics. A useful sign is the development of an acute epigastric pain on sharply punching the lower ribs in the right axillary line.

Icteric Stage

The appearance of jaundice is usually accompanied by some improvement in the subjective well-being of the patient. In severe cases the jaundice is frankly obstructive, the stools are clay-coloured, and constipation is troublesome. In mild cases the stools may remain normal in colour, but in every case the obstructive nature of the jaundice declares itself by the appearance of bile pigment in the urine.

Nearly all cases run a benign course, the jaundice and symptoms gradually subsiding in one to three weeks. When the jaundice has completely cleared and the patient is becoming convalescent there is a well-recognized tendency to relapse and the reappearance of the jaundice. These patients usually make a complete recovery after a further period of rest in bed. A more serious variation from the usual course is for the jaundice to persist for several weeks or months. This is often associated with progressive and permanent liver damage, culminating in hepatic cirrhosis. This sequence

of events occurs in about 0.5 to 1% of cases. A somewhat greater proportion, some 1–2%, after making an apparently complete recovery, relapse some months later. The clinical course in relapse tends to be more severe than in the first attack, and permanent sequelae are probably more frequent.

The most serious, and often fatal, deviation from the common benign course is the onset of acute yellow atrophy. This complication is usually heralded by evidence of cerebral disturbance with delirium subsequently declining into coma and often followed by death. Reduction in the area of hepatic dullness is commonly described, and sometimes the appearance of a haemorrhagic tendency, with bleeding particularly from the mucous membranes. These most serious symptoms are strongly suggestive of massive hepatic necrosis, and call for strenuous therapeutic measures if death is to be averted.

Differential Diagnosis

In the midst of an epidemic diagnosis in the icteric phase is fairly obvious. In the pre-icteric phase the diagnostic problem is that of pyrexia of unknown origin. At this stage the pronounced loss of appetite, abdominal pain and tenderness in the right upper quadrant, and the appearance of urobilin in the urine are points of greatest significance.

Once jaundice has appeared the chief problem of the physician is to distinguish infective hepatitis from other causes of jaundice associated with biliuria. Toxic jaundice resulting from exposure to liver poisons such as carbon tetrachloride or T.N.T. can usually be excluded on the history. Weil's disease, or spirochaetal jaundice, is usually associated with a rat-infected environment; and, clinically, severe conjunctival injection, herpes labialis, and albuminuria are characteristic. Moreover, excellent laboratory diagnostic methods are available—namely, the isolation of the causative spirochaete from the blood or urine in the early stages, and the serum-agglutination tests later on. Infectious mononucleosis, or glandular fever, may also be associated with jaundice and a clinical picture much like that of infective hepatitis. A blood count is not very helpful, as a moderate lymphocytosis and mononucleosis is also common in hepatitis. A positive Paul–Bunnell heterophil agglutination test will, however, readily identify the cases of glandular fever after the first week.

Jaundice due to obstruction of the extrahepatic bile ducts may prove extremely difficult to differentiate from infective hepatitis, especially those cases of hepatitis in which the jaundice persists for more than three to four weeks. This differentiation between obstructive and parenchymal jaundice is a major diagnostic problem, as the treatment of obstruction is mainly surgical and that of hepatitis entirely medical. It is mainly for this type of case that the large variety of so-called liver-function tests have been developed. It must, however, be emphasized that no single laboratory test is infallible, and when one considers the damage to the hepatic parenchyma that must inevitably result from several weeks of biliary obstruction it is hardly surprising that cases of biliary obstruction may show evidence by these tests of parenchymal change. Nevertheless their diagnostic usefulness has been amply demonstrated, and when combined with the clinical data and history a correct diagnosis may be reached in well over 90% of cases. As most liver-function tests require adequate laboratory facilities, and since, moreover, surgical intervention is required for nearly all cases of obstructive jaundice, it is advisable that all suspected cases of hepatitis that remain jaundiced for longer than one month should be transferred to hospital for further investigation.

Prognosis

In most cases the prognosis is excellent, complete recovery without sequelae occurring in over 90%. The immediate mortality among the otherwise healthy and well-nourished is approximately 0.2%. But in 1–2% there is chronic liver damage, with persistence of hepatic enlargement, slight jaundice, which waxes and wanes, and permanent impairment of health usually terminating months or years later in hepatic cirrhosis with ascites. Clinical evidence of chronic parenchymal damage may usually be found in these patients. Pulsating spider naevi on the face, hands, and arms and a mottled erythema of the palms and soles may be seen in cases of either sex. In men, loss of hair on the chest, gynaecomastia, and testicular atrophy with loss of libido may also occur, while in women menstrual disturbance, especially menorrhagia, is not uncommon. All these disturbances are thought to result from an excess of circulating oestrogens owing to impairment of the liver's normal capacity to inactivate these hormones. Slight oedema of the ankles, with hypoproteinaemia and reversal of the albumin/globulin ratios, and a moderate degree of anaemia, sometimes of macrocytic type, are also indicative of the progressive failure of the liver in these chronic cases.

Certain factors seem to predispose the individual to a severe attack. Malnutrition is probably a major factor in the high mortality observed in outbreaks among the native populations in less well nourished communities of the world; mortality rates up to fifteen times those occurring in healthy European communities have been reported. Previous severe injury or burns also appear to affect the prognosis adversely, and were probably responsible for the unusually high mortality rates in some of the published reports on Service personnel in the last war. Pregnancy also seems to impose considerably increased risk of acute yellow atrophy in patients with infective hepatitis.

Malnutrition, recent injury, and pregnancy all have in common a considerable disturbance of protein metabolism, and, in the light of recent experimental work on the production of massive hepatic necrosis by diets deficient in protein, it has been suggested that a similar metabolic disturbance may be at work in these hypersusceptible cases.

Treatment

There is at present no specific chemotherapeutic agent operative against the virus of infective hepatitis. The extensive epidemics of recent years, however, have provided excellent opportunities for therapeutic trials of several regimes, and have resulted in considerable uniformity of opinion about the best methods of reducing the duration of disease and the likelihood of sequelae.

Rest in bed for as long as the jaundice persists is probably the most important of all the therapeutic measures. With the disappearance of bile from the urine the patient may be allowed to leave his bed for purposes of toilet, but rest in bed should otherwise be maintained until any hepatic enlargement and tenderness have virtually disappeared. Return to full activity should be gradual, as many cases relapse if this precaution is ignored. After

a period of two to three weeks in bed, at least a fortnight should be allowed for convalescence.

Recent experimental work has emphasized the importance of protein in maintaining the integrity and function of the liver. Fatty diets, however, have been shown to enhance the toxicity of several liver poisons. There is therefore general agreement that the patient's diet should be rich in protein and carbohydrate, but poor in fat. If, however, fat be too severely restricted, the meals become unpalatable. A daily diet containing 150 g. of protein, 350 g. of carbohydrate, and 50 g. of fat will provide about 2,500 calories, which is ample for a patient confined to bed. As the appetite is impaired and nausea and vomiting are common, meals should be small but be given at frequent intervals. If dehydration occurs from excessive vomiting parenteral fluid and even parenteral feeding may have to be used.

There is little evidence that supplements of methionine, cystine, or choline will affect the duration of the disease in subjects who were previously healthy. It is, however, possible that, in the previously malnourished, supplements of the sulphur-containing amino-acids may reduce the mortality from acute yellow atrophy. These are most conveniently given as methionine in tablet form in a daily dosage of 3–5 g.

Patients in whom little bile is reaching the intestine may have difficulty in their absorption of fats. Such patients on a low-fat diet may suffer from deficiency of fat-soluble vitamins. This is unlikely to become manifest in acute cases, but in those in which the symptoms persist for several weeks vitamins A and E should be given, and vitamin K also if the plasma-prothrombin level is low. Vitamin A may be given in daily doses of 25,000 to 50,000 units, and vitamin E in a daily dose of 100 mg.

Of the water-soluble vitamins, ascorbic acid will probably be adequate provided the diet contains, as it should, a reasonable amount of fresh vegetables and fruit. The water-soluble vitamins of the B complex are very intimately associated with liver metabolism. Since an imbalance of these vitamins may well result from supplementation with the known pure preparations, a cheaper and more satisfactory means of achieving the same end may be obtained by giving a crude liver or yeast extract.

Apart from rest and careful dietary supervision, the treatment of infective hepatitis is largely symptomatic. Constipation, which may be troublesome, especially when very little bile is reaching the intestines, is best dealt with by saline laxatives. If a sedative is required barbiturates and opium alkaloids are best avoided, as their detoxication and excretion are largely dependent upon normal liver function. Chloral hydrate and paraldehyde are undoubtedly the safest. Nausea and vomiting may be very resistant to treatment, but small meals and attention to the bowels are usually sufficient to avoid the necessity for more drastic measures. In extreme cases it may be necessary to feed the patient parenterally. Alcohol should be strictly avoided, both during the disease and preferably for several months afterwards.

Relapses and remissions should be treated in the same way as first attacks, but return to full activity should be slower, as such relapses considerably increase the risk of permanent hepatic damage. Pre-coma and coma require treatment that is quite beyond that usually attainable in the home. If it is thought that coma is likely to develop the patient should be transferred to hospital as soon as possible.

PUBLIC HEALTH ON SHOW

The art or craft of exhibiting, which has been brought to a new high level in the Festival of Britain, is well exemplified in a display which is open for this summer at the London School of Hygiene and Tropical Medicine. Here, superimposed on the interesting permanent museum of the school, on the second and third floors at Keppel Street, there has been arranged a display which advertises some of the achievements in public health and social welfare of the last 100 years, and particularly of the last 50. In its arrangement, in the way the story is told, it is wholly admirable. All the means available to the modern exhibitor have been used—attractive text, catchy slogans, pointed cartoons, comparative photographs, telling diagrams and charts, and ingeniously designed models. Sometimes no text is necessary; the pictures themselves are enough. In the section concerned with child health, for example, two photographs are shown side by side. One of them is of a group of boys in a Southwark school in the 'nineties, the other of a similar group in the same area 50 years later. The contrast is impressive. It is evident that the boys in the earlier picture are ill nourished; they appear dull, listless, vacant in expression; some are obviously defective; a number appear to be adenoidal, whereas in the other photograph almost all the boys are bright and alert, well nourished, and well clad. But many of the exhibits in this section take one back to an earlier period, when large numbers of children, especially in industrial areas, had no childhood—the time of W. P. Frith's "Crossing Sweeper" and Shaftesbury's ragged schools. When the Great Exhibition was opened, infant mortality in this country was something like 158 per 1,000 births; in the last quinquennium it was below 40 per 1,000. Other photographs trace the evolution of welfare centres from the early shacks in which some of them were housed to the modern well-equipped building. They also tell the story of the beginnings of school medical inspection and the school dental service.

The National Health Service

One large exhibit of many panels introduces us to the ramifications and interrelations of all that is comprised in the National Health Service. The chart of the services and administrations and how they are derived and the relation they bear to one another looks rather like a map of London underground transport. One of the panels is devoted to the family doctor. Here we are told that circumstances will not allow the general building of health centres for many years to come, but that there is urgent need to improve the conditions under which general medical practice is carried on. The encouragement of group practice, it is pointed out, could foster such improvement. "The family doctor is the basis of the National Health Service." The work of the medical officer of health is also well depicted in his relation to the health, welfare, education, and children's committees of his local authority, and photographs illustrate his manifold activities. Some attempt is also made to indicate the organization of the hospital services in a region. Then there are the ancillary services, each with its appropriate pictures—the Public Health Laboratory Service, organized by the Medical Research Council; the immunization service, carried out by the local authority and family doctors; the transfusion service, for which regional hospital boards are responsible; and, finally, mass miniature radiography.

Nutrition in West Africa

Some experimental researches in public health are portrayed with an ingenuity which fastens them on the lay mind. These include comparative studies of health and of ages at death of people of tropical and of temperate climates, and the difference which the conquest of malaria has made in the Tropics (Ceylon). A large section is devoted to setting out graphically what is called an experiment in human nutrition. During the last few years an effort has been made to raise the standard of life of the

people of Gambia, to improve their nutrition, protect them against disease, and at the same time strengthen their economy and develop self-reliant communities. A clinical survey made at the beginning of the effort showed that a considerable proportion of the population showed signs of malnutrition. Accordingly agricultural supplies were improved, more land was cultivated, production methods stepped up, and qualitative studies of diets were made. Gradually, with improved farming and more food, a better nutritional state has developed, in particular a better growth pattern in the young, though a balanced economy and a balanced agriculture still remain to be achieved.

Research Exhibits

Other panels set out the story of the epidemiology of the common cold, on the basis of a survey made among Post Office workers—a story which has to be continued in an uncertain "next." Another exhibit shows the association between heavy cigarette smoking and the increased incidence of lung carcinoma; another depicts the experiments with streptomycin in tuberculosis; yet another is called a study in bacterial detection—the "fingerprinting" of types of bacteria within the species so as to assist in tracing the source of epidemics. This exhibit shows the application of phage-typing of typhoid bacilli in field entomology.

Then, of course, there is housing, which lends itself best of all to exhibition. Successive groups of photographs and tables and other matter suggest what an immense rehousing problem was created by the second world war, the phase of improvisation which followed, and the beginnings of planning. The housing of the Londoner, of the people of smaller towns and cities, and of the countryman is displayed, also experiments in the housing of special classes such as the old and the disabled, and finally the making of the new towns. It is stressed that what is called the housing problem concerns much more than the putting up of a decent shell; it concerns the design of the kitchen, the bathroom, and other parts of the house, and the choice and disposition of the furniture.

The exhibition at the London School is not as spectacular as others associated with the Festival, but it comes closer home than most, and in its arrangement it is as ingenious as any. At the same time the visitor will see many interesting things in the permanent collection, including material relating to the great pioneers in public health whose names are engraved around the top of the building. The exhibition is open to medical practitioners and students.

The Medical Act, which reached the Statute Book in August, 1950, affects the University of London in several ways (*Principal's Report for the Year 1950–1*). The General Medical Council now has the power not only to inspect medical examinations but also to visit medical schools; the Council's visits are expected to coincide with the Senate's inspections. By Order in Council a medical student must now, following registration, serve for a short period as an intern in an approved hospital. The University has prepared a list of hospital posts in the four metropolitan hospital regions which it considers suitable for the purpose. Hitherto it has been possible to obtain exemption from the Internal First Medical Examination either through the Higher School Certificate Examination or by passing the corresponding external examination. The Faculty of Medicine has long wished to link the first and second medical courses, and agreement to do so has now been reached in principle. This causes practical difficulties of staffing and accommodation, and the Senate has decided to introduce the new system in a limited number of schools. From October, 1953, some medical schools will be bringing into operation the new integrated preclinical course, from which no exemption can be gained by passing another examination. The remaining schools will work under the old regulations until the difficulties in adopting the new system are overcome.

JENNER MEMORIAL MEDAL

PRESENTATION TO DR. J. ALISON GLOVER

On May 18, in the presence of members and guests of the Section of Epidemiology and State Medicine of the Royal Society of Medicine, Lord WEBB-JOHNSON presented the Jenner Memorial Medal to Dr. J. Alison Glover. The medal was instituted by the Epidemiological Society of London (of which the Section of Epidemiology is the direct descendant) on the occasion of the Jenner Centenary Celebrations in 1896, and is awarded for distinguished work in epidemiological research or for pre-eminence in the prevention and control of epidemic disease. Dr. Glover is the eleventh recipient of the medal.

Research on Cerebrospinal Fever

Dr. W. H. BRADLEY, President of the Section, recalled Dr. Glover's outstanding contributions to the science of epidemiology. In 1918 Dr. Glover had applied Gordon's classical work on the types of the meningococcus to the study of carrier rates in a community. He had shown that a high carrier rate denoted overcrowding and lack of ventilation in the community in which it was found; that this high carrier rate took from two to three weeks to develop after overcrowding had begun, and that any intercurrent respiratory disease, by increasing the spraying capacity of the carriers, was a powerful accelerator. Although sporadic cases of cerebrospinal fever might occur with any carrier rate, anything approaching an epidemic of cerebrospinal fever would be heralded by a warning rise of considerable height in the carrier rate. This work powerfully reinforced the opinion of military medical officers against overcrowding and caused the then director of pathology to report: "He [Glover] has been a good friend to the private soldier." Dr. Glover also did the bacteriological part of the work which enabled Clemenson to describe the nature of the nasal deformity which almost invariably characterizes the common carrier of the meningococcus. He also showed the remarkable variations in potency of various batches of anti-meningococcus serum.

The Rheumatic Diseases

Dr. Glover was appointed secretary of the first rheumatism committee set up by the Ministry of Health, which had organized the successful general-practitioner inquiry into the incidence of rheumatic diseases among insured persons. The committee's report on "The Incidence of Rheumatic Diseases" was published in 1924, and there was little doubt that it had given the primary impetus to the formation of the international league against rheumatism, and it had been one of the main points in the appeal for the foundation of the British Red Cross Clinic for Rheumatism at Piccadilly Place. The report was still characterized by the American Committee for the Control of Rheumatism as being basic.

Dr. Glover had been one of the first to describe outbreaks of acute rheumatism in semi-closed communities and to demonstrate the silent carrier-wave of haemolytic streptococci, with the visible wave of tonsillitis preceding by 10–14 days the individual cases of acute rheumatism in the outbreak. With the late Fred Griffith, Dr. Glover had published several papers on outbreaks of nasopharyngeal infections in boarding-schools and shown the importance of proper spacing in the control of these; he also demonstrated the aetiological identity of tonsillitis, pharyngitis with unnoticeable sore throat (febricula), and scarlet fever, and had associated these conditions with otitis media and acute rheumatism. These observations did much to lead Okell to the "unitarian view" of infection by *Streptococcus pyogenes*. He had also written on infectious hepatitis, on dysentery, and largely on the tonsil problem.

In all this work Dr. Glover's concern had been for the sick person and had been directed towards the prevention of disease. That was what they would expect from such

a sensitive, generous, and affectionate man. In latter years these qualities had endeared him to an ever-increasing circle. As editor of the Report of the Chief Medical Officer on the State of the Public Health in the annual *Report of the Ministry of Health* for the past 11 years, and as editor of the *Monthly Bulletin of the Ministry of Health and Public Health Laboratory Service* since its first appearance in 1943, Dr. Glover's kindness had brought relief to a large number of young and discouraged authors.

Dr. Glover's Reply

In reply, and after expressing his gratitude and appreciation of the award of the medal, Dr. GLOVER said that of the ten previous recipients he had known seven. Two—Laveran and Manson—were among the immortals, their names graven in stone upon the frieze of the London School of Hygiene and yet more indelibly stamped upon the history and nomenclature of disease. Two—Power and Newsholme—had been distinguished epidemiologists as well as chief medical officers of the Local Government Board; two were medical statisticians—Stevenson, the finest vital statistician since Farr, and Major Greenwood, the co-founder of experimental epidemiology. Two others—McVail and Copeman—had rendered great services to Jennerian vaccination. Of the two under whom he had had the honour to serve, Sir George Buchanan might well be termed the father of international health, while Sir Shirley Murphy had not only written a famous textbook of public health but also, while he was Chief Medical Officer of the London County Council, had put all Londoners for ever in his debt by his influence upon the building by-laws.

All these were dead, but their work survived them in many a classic report and standard textbook. He himself had been nurtured in preventive medicine by a father, a friend of Lister and his early supporter in the columns of the *Lancet*, who, as a port cholera officer, had seen the last great cholera epidemic here in 1854, a year when 10,000 persons died of cholera in England and Wales. Dr. Glover ended by paying tribute to the host of able friends to whom was due, he said, the credit for any contribution to epidemiology which he had been able to make.

ROYAL CANCER HOSPITAL

CENTENARY CELEBRATIONS

The Royal Cancer Hospital celebrated its centenary last week by opening its doors to visitors from May 15 to 18. At the Chester Beatty Research Institute there was an impressive display of the work of scientific investigation which goes on side by side with the more publicized activities of the therapeutic departments. On May 16 the chairman and board of governors gave a reception at the hospital at which the Duchess of Gloucester was present, and on May 17 a dinner was held at the Hyde Park Hotel. After the chairman, Sir EDWARD CRIPPS, had read a message of congratulation from the King, Sir HENRY DALE proposed the toast to the hospital. He briefly reviewed the history of what he called this "humanitarian enterprise," which had now become a centre of research and teaching. Mankind had perverted the benefits of science to increasingly horrible methods of destruction, but, by way of compensation, medicine and physics had been able to divert to life-saving uses discoveries which would have been made only much later had it not been for the urgent pressure of war. After discussing the attack on cancer which was converging from many directions, Sir Henry said that in the last 50 years there had been a great change for the better in the conquest of disease, with sudden turns from frustration to success. Persistence in research would ultimately lead to success in cancer.

In reply, Lord HORDER, who was appointed to the staff of the hospital as its first physician in 1908, said that the Royal Cancer Hospital had amply justified the aims of its founder, and mentioned some of the men who had helped to bring it to the fore. The special hospitals in general and the Royal Cancer Hospital in particular had made immense contributions to pathology and medicine. The British Empire Cancer Campaign showed its confidence in the value of the research work being done at the Royal Cancer Hospital by the funds which it granted for the furtherance of this research. Lord Horder ended his speech with a plea that the governors might again consider the advisability of changing the name of the hospital to avoid emphasis on the word cancer.

The health of the guests was proposed by Mr. OLIVER LYTTELTON, and in reply Mr. H. A. MARQUAND, the Minister of Health, said that not only this country but also the Commonwealth was justly proud of the Royal Cancer Hospital. The recent change of ownership was not intended to be a change of function or purpose. The deadliness of the foe faced by the staff of the hospital was in itself a challenge to them. Hope for the future lay in research, and he intended that the Ministry should give all the help it could in that direction. Mr. Marquand also mentioned the necessity of overcoming the public's fear of cancer, and said that films were being prepared with the help of the Royal Cancer Hospital to show that there was a real prospect of successful treatment in certain cases.

SANITARIANS IN CONGRESS

MANIFOLD ASPECTS OF PREVENTIVE MEDICINE

Delegates from about 800 local authorities, as well as from Government departments, overseas Governments, the World Health Organization, and other interested bodies, assembled at Southport from April 23 to 27 for the Health Congress of the Royal Sanitary Institute. The British Medical Association was represented by Dr. C. Metcalfe Brown and Dr. J. M. Gibson. The Congress divided its work among eight sections, and there were special conferences for medical officers of health, engineers and surveyors, sanitary inspectors, and health visitors. The subjects ranged over preventive medicine, maternal and child health, food and nutrition, and industrial hygiene, and included such themes as the human element in the planning of new towns, the design of a premature-baby unit, and occupational diseases of interest to engineers and surveyors—namely, Weil's disease, silicosis, and occupational dermatitis.

Rheumatic Diseases

The Preventive Medicine Section was presided over by Sir JOHN CHARLES, who devoted his address from the chair to an appraisement of John Simon and his contemporaries, especially William Farr. Sir HENRY COHEN opened a discussion on rheumatic diseases, a subject, he said, which had suffered from vague differentiations, leading to woolly thought and the gathering of worthless statistics. He suggested the following classification, based on present knowledge: (1) arthropathies (*a*) of known cause (infective, metabolic, haemorrhagic, neurogenic, traumatic), (*b*) of unknown cause (acute and subacute rheumatism, rheumatoid arthritis, osteoarthritis), and (2) non-articular rheumatism (myositis of known and unknown origin, "fibrositis," "panniculitis," "neuritis," etc., and skeletal disease, such as disk lesions). He estimated that there were in Great Britain at least 250,000 arthritics, costing the community in loss of productive capacity hundreds of millions a year, but when the cry of "cortisone for all" was raised it was well to remember that, at $35 a gramme, assuming an average dose of 100 mg. daily, the treatment of one patient would cost £450 a year, even if such large amounts of the drug were available. The increasing appreciation of the importance of rheumatic disease was due, among other factors, to Lord Horder's zeal in forming the Empire Rheumatism Council, to the Heberden Society, and to the interest of the Nuffield Foundation and the Medical Research Council.

Dr. E. T. CONYBEARE (Ministry of Health) said that the prevention of acute rheumatism would elude us until its aetiology was more completely understood, but a concerted

attempt was being made to tackle this problem in several areas where acute rheumatism was notifiable. Inquiries had been inaugurated by the Rheumatic Fever Committee of the Royal College of Physicians along lines laid down by the late Professor Ryle. There was good evidence that large doses of penicillin by mouth would prevent Group A streptococcal infection in those exposed to it. A trial of penicillin prophylaxis was now being made at the rheumatism supervisory clinic in Bristol. The Medical Research Council had set up a panel to evaluate the place of hormones (cortisone and A.C.T.H.) in the treatment of acute rheumatic disease, in co-ordination with similar work in the United States.

Food Infections

In the Section of Veterinary Medicine an interesting paper was read by Dr. W. S. DAVSON (Birmingham) on the three animal parasites apt to be found in British abattoirs and infectious for man. The first of these was *Trichinella spiralis*, which inhabited the small intestine of pigs. This parasite was killed by heat, and it was worth remembering that, while pork was usually fairly well cooked, sausage meat, ham, and bacon were often eaten raw or partially cooked. An outbreak in Wolverhampton in 1941 was traced to raw or uncooked pork. The others were *Cysticercus bovis*, which was not extinct in this country as was commonly supposed, and *Cysticercus cellulosae*, which seemed to be virtually extinct—at least the only well-authenticated case of infection by this parasite, over several years, was at Hitchin in 1949. There was room for investigation and research in all these matters, both by the medical authority as represented by the Ministry of Health and by the food inspection service as represented by the Ministry of Food.

Dr. E. R. CALLENDER (Ministry of Agriculture) gave figures concerning the eradication of bovine tuberculosis. The number of attested herds, which 15 years ago was only a few hundred, was now over 55,000.

The question of emulsified food products was the concern of another Section. It was stated that since the Heat Treatment Regulations came into force in 1947 only a few minor outbreaks of food-poisoning due to ice-cream had occurred, but synthetic cream, which was becoming more popular, had been responsible since 1942 in England and Wales for 14 outbreaks of bacterial food-poisoning and three of paratyphoid fever.

Adopted Children

Dr. ALFRED TORRIE, speaking as a mental health expert, gave some excellent advice to another Section concerned with the placement of adopted children. He warned magistrates and others that to judge the suitability of prospective parents only by their economy, the spotlessness of their house, and the number of its rooms was to miss half the problem. The plain gruff woman who had little to say for herself might have a capacity for developing affection and might make a most successful substitute mother; and a home not too spotless from the health visitor's standpoint might have parents capable of a relationship emotionally satisfying to an adopted child.

Concern was expressed at another meeting at the short supply of health visitors. They number 2,534 full-time and 7,021 part-time. The number of domiciliary midwives, which is comparable, is probably sufficient in view of the increase in hospital confinements, but the pool of female labour of the age group from which health visitors are recruited has been greatly reduced during the last 10 years, yet a full health visiting service for the family was promised under the Act.

The relationship of the child-welfare officer and the school medical officer to the National Health Service was the subject of several papers. Dr. A. V. NEALE (Birmingham) said that there was nothing more satisfying than a general practitioner who had a practical and comprehensive outlook on the whole family. He hoped that a gradual easing of conditions of general practice would enable a not overworked doctor to take a positive interest in welfare work. Dr. R. W. ELDRIDGE (Lancashire C.C.) pleaded for a strengthening of the tie between the school medical officer and the hospital, perhaps by making the school medical officer responsible for some paediatric out-patient sessions.

Among the medical officers of health a good deal was said about the loss of clinical responsibility, but as one of them (Dr. W. S. PARKER, Brighton) remarked, although the complexities of modern local government had chained the medical officer to his desk, the true field of his work opened out more and more in the cultivation of the mental and physical health of the community.

EMERGENCY BED SERVICE

REPORT FOR THE YEAR ENDED MARCH 31, 1951

The first half of the year saw the continuance of the steady and regular increase of work which has been evident ever since the service has worked for the regional boards. However, there is reason to hope that this trend is gradually stopping. This hope springs from the fact that for the month of November, 1950, the applications were nearly the same as in the previous year. Then came the influenza epidemic, which was quite exceptional, but when in March the epidemic ended the figures reverted to the level of the previous year.

The Influenza Epidemic

The influenza epidemic produced a strain on the service hitherto quite unknown. For not only did the resultant acute cases, mainly of respiratory diseases, increase the demand for acute admissions by 35%, but also there were epidemics of measles, whooping-cough, and chicken-pox, which resulted in a 92% increase in fever applications. In all, this resulted in 2,380 applications of all sorts being received in one week in January. The previous highest weekly total was 1,660 on February 2, 1950.

To cope with this burden it was found necessary to evolve some way of curtailing the number of applications for medical cases, and to this end the system of "Restricted Approach" was brought into force. This meant that, on days when hospitals were believed to have reached saturation point for a certain type of case, a general practitioner asking for a bed was advised of the situation and asked whether his patient could possibly wait until the following day. If this proved impossible, the case was taken on by the service and the nearest hospital approached for a bed. If this failed, the regional medical admissions officers were consulted for instructions. Thus, as during the previous winter, no case was actually refused. The number of applications for acute medical and surgical cases only during the whole of January was 7,064 compared with 5,718 for January, 1950, an increase of 35%. During this time the number of admissions failed to keep up with the applications, and for the whole of January the admissions were only 65% of the applications, a figure 10% below that for the corresponding period the previous year. At the worst point, the failure rate was about 100 per day. In addition to this, epidemics of infectious diseases were in progress, so that the *total* applications of all kinds for January came out at 9,900.

New Warning System

This threw a very great pressure on the service, although the regional boards took all the steps open to them to overcome the difficulties of this crisis, which undoubtedly prevented the crisis from being even more serious than it was. However, it was evident that more could have been done if an efficient warning system had been in existence, and for future use a scheme is in preparation based on an adaptation of the air-raid warning system which will come into operation automatically on a prearranged plan as the pressure on the emergency bed service begins to mount. A preliminary warning will be sent to the regions when the

percentage of admissions falls below 80%. On its falling to 75% a further warning will be sent out and relayed by the regions to all hospitals and by the Ministry of Health to all teaching hospitals. On its reaching 70% another warning will be similarly dispatched. The actual steps to be taken by the hospitals on receipt of these warnings will be a matter for mutual arrangement between the hospitals and the boards. The duty of the service will lie in ensuring that prompt warning is given.

Details of the Applications

The total number of applications received during the year ended March 31, 1951, and the corresponding figures for the previous year were as follows:

	1951	1950
General acute cases	49,573	42,732
Infectious cases	17,445	14,506
Chronic sick cases	4,196	3,411
Total	71,214	60,649

The 1951 figures show a percentage increase of 14.8%.

Acute Cases

Of the 49,573 cases offered, admissions were 40,560, an increase of 5,985 on the previous year. Cases withdrawn by the applicant totalled 1,617 plus 205 not taken on under the system of "Restricted Approach." For the remaining 7,191 no beds could be found, and these were referred back to the applicant. In 1,134 of these cases the applicant was a hospital and the patient was in the casualty department but could not be admitted to the wards owing to the lack of beds.

Comparing the winter months (November to March inclusive) of 1949–50 with those of 1950–1, the number of cases admitted shown as a percentage of cases offered was 77.5% for 1949–50 and 76.4% for 1950–1. The worst months in each winter were January and February, when 75% were admitted in each case in 1950 and 65% and 75% respectively in 1951.

Once again this winter there was some difficulty in admitting patients over 60 years, and, although the situation has shown improvement over that of the previous winter, the percentage increase in these age groups has not been as great as that of 1950 over 1949. There has been a drop in the percentage of admissions in the age groups from 30 to 60 years, but as the percentage of admissions as a whole fell in January, 1951, 10% below that of January, 1950, this decrease is accounted for.

General Practitioners' General Acute Cases Only, November 5, 1950, to February 24, 1951

Age Group	Cases Offered	Percentage Admitted	Percentage Increase or Decrease Compared with 1949–50	Percentage Increase or Decrease Compared with 1948–9
Birth–20 ..	3,403	98·4	0·3	—
21–30 ..	1,660	95·6	0·4	−0·1
31–40 ..	1,572	94·2	−0·8	0·5
41–50 ..	1,858	88·2	−3·7	0·2
51–60 ..	2,631	79·9	−3·5	2·5
61–70 ..	3,571	71·5	−0·4	5·7
71–80 ..	2,729	62·1	0·2	6·9
Over 80 ..	879	53·1	2·1	8·1
Total offered	18,303			

Infectious Cases

Infectious cases have proved somewhat more difficult to admit than before, and in the winter months it was found necessary to impose restrictions on cases of measles, chickenpox, and whooping-cough. With the co-operation of the public health authorities those infectious cases with medical complications and those whose home conditions were unsuitable were given a degree of priority. During the winter, 183 infectious cases had to be referred to the group medical referees before securing admission.

Chronic Sick Cases

The machinery for dealing with chronic sick cases remains unchanged. The branch offices are responsible for keeping the files of chronic cases placed on the waiting-lists and for dispatching the details of each case to the appropriate hospital management committee. These details are sent out on the day of application so that there is as little delay as possible.

Group Medical Referees

Of the general acute cases admitted 1,620 had to be referred to the group medical referees before it was possible to find a bed for them. This represents a percentage of 3.26% of the total applications over the whole year. The worst month was January, when 357 general acute cases and 61 infectious cases were admitted by the medical referees; this put a great strain on the system. Without their co-operation the position would have been much more difficult.

Time Taken to Deal with Cases

There has been a further reduction in the time taken to deal with cases. The previous winter the average time needed to admit a case was 42 minutes. This winter it has been reduced to 34 minutes, in spite of the greatly increased number of cases with which the emergency bed service has been called upon to deal. In each case it was found necessary to approach an average of 3.02 hospitals in order to obtain admission in comparison with 3.36 the previous winter.

Where the patient was not admitted the average time taken to conclude the case in the winter of 1949–50 was 2 hours 25 minutes, in the course of which 7.05 hospitals were tried. This year the average time was 1 hour 31 minutes, during which time 5.56 hospitals were approached before the case was handed back. These averages were taken over a sample week in February and are for all cases dealt with in Greater London. This reduction, unfortunately, does not represent a greater facility in dealing with cases. The reason for it is that the regional medical admissions officers have been asked to give a decision for or against the admission of cases at an earlier stage.

Branch Offices

The branch offices, which were opened in the autumn of 1949, are now firmly established. They have dealt with 47% of the total number of applications in comparison with approximately 42% the previous year. This increase is largely due to the extension of their areas of operation to include some of the boroughs previously allotted to Old Jewry. In addition, they are being more widely used by the local general practitioners. It is difficult to assess the percentage increase, as the offices at Leytonstone, Ealing, and Woolwich have been in operation only since October 3, 1949, and that at Wimbledon since November 5, 1949. The figures for 1949–50 cover only the winter months. During the past year (1950–1) they have dealt with the following cases:

	General Acute	Infectious	Chronic	Total, 1950–1	Total, 1949–50
Leytonstone ..	8,257	1,384	1,330	10,971	5,058
Ealing ..	4,572	758	1,146	6,476	3,561
Woolwich ..	5,992	1,795	708	8,495	4,617
Wimbledon ..	5,261	1,699	867	7,827	3,398
Total, 1950–1 ..	24,082	5,636	4,051	33,769	
Total, 1949–50	12,269	2,410	1,955		16,634

Speaking at the Royal Sanitary Institute's congress at Southport on April 24 Sir Henry Cohen said, according to the *Scotsman*, that it was well to remember when the cry of "cortisone for all" was raised that it cost $35 a gramme. The treatment of 250,000 patients would thus cost £112m. a year.

Correspondence

Paralytic Ileus after Hexamethonium

SIR,—C. Hirson and A. R. Kelsall (*Lancet*, 1951, **1**, 585) report a death which they ascribe to "paralytic ileus" during treatment with hexamethonium compounds. We have recently encountered a similar case.

A man aged 66 was admitted to hospital. He was hypertensive (blood pressure 205/110) and had recently been the victim of a left-sided cerebrovascular accident. He showed grade II retinopathy, but his renal and cardiac state appeared satisfactory. He had a hyper-acid dyspepsia with pylorospasm. With bed rest, blood pressure fell to 175/110. Hexamethonium therapy was cautiously begun and he was discharged after 18 days on an oral dosage stabilized at 500 mg. thrice daily. He appeared to have improved greatly during his time in hospital. His residual paralysis had almost cleared and his blood pressure had fallen to 148/82 recumbent, 140/70 standing. At the out-patient clinic a week later, he reported that he was rather constipated. His blood pressure was a few points higher than on discharge. One month later his blood pressure had further risen to 188/110 recumbent, 164/106 standing. He was less troubled with constipation, but noticed that his mouth was dry. The dose of hexamethonium was increased from 1.5 to 1.75 g. a day.

A week later he became nauseated. Next day he began to vomit bright green fluid and had some diarrhoea. His practitioner noted that his pulse was feeble and his blood pressure unrecordable. He immediately stopped methonium therapy, but the blood pressure did not rise. After two days of vomiting the patient was readmitted. He was severely dehydrated and his abdomen was distended. Occasional faint bowel sounds were heard. His blood pressure remained unrecordable and he died one day later.

Necropsy was carried out by Dr. Archibald Dick, who reported: "Hypertensive disease of moderate severity as evidenced by changes in heart and kidney. Generalized atheroma. Area of softening in left cerebral hemisphere as result of old thrombosis. The most interesting features were found in the alimentary tract—namely, stomach grossly dilated with bile-stained fluid; mucosa somewhat atrophic with numerous small erosions in middle third and pyloric region; slight degree of pyloric stenosis due to considerable scarring from healed duodenal ulcer. Common bile duct entered duodenum unusually high up. Small intestine, particularly jejunum, was grossly dilated with appearances of a paralytic ileus, there being much congestion and oedema, while a considerable amount of fluid filled the lumen; no mucosal ulceration was found. No distension or other abnormality noted in colon. Histologically the stomach showed slight superficial necrosis but little cellular infiltration, and, as necropsy was performed fifteen hours after death, post-mortem autolysis probably caused this. The jejunum and ileum showed very marked necrosis of the mucosa; submucosa oedematous and blood and lymphatic vessels being dilated. Appearances were consistent with a pressure necrosis due to accumulation of fluid and gas in the intestine. Little inflammatory cellular reaction; no abnormality noted in ganglia in small intestine."

It seems highly probable that this patient's death was immediately attributable to C6 therapy. The mechanism is obscure, but is presumably related to a profound disturbance of the control of blood pressure and exchange of electrolytes.—We are, etc.,

W. ARTHUR MACKEY.
GAVIN B. SHAW.

Glasgow.

First Mention of Rickets

SIR,—Under this heading Mr. F. N. L. Poynter (May 12, p. 1081) quotes Thomas Fuller's reference to rickets (1647), which he suggests has not yet met the eye of the historian of the disease. This is not so. The passage from the 1649 edition is quoted and commented upon in Drummond and Wilbraham's *The Englishman's Food* (1939, pp. 187 and 188). The relevant section in the 1647 edition (number "XX") is entitled "The new disease"; it differs in minor points from the passage given by Mr. Poynter.

There are, of course, earlier mentions of rickets in English. "The new disease" is not, I think, mentioned in the weekly Bills of Mortality (which started in 1592 and were resumed in 1603) until the year 1634; thereafter the word "Rickets" appears almost continually among the list of "Diseases and Casualties." There is much evidence that the disease suddenly became prevalent in England during the first 20 years of the 17th century: Whistler (1645), Fuller (1647), Glisson (1650), Sir Thomas Browne (about 1650), and others suggest this. But it is obscure why this should have been so; and at the middle of the century certain remedies were quoted as if they had been in use for some time (Browne states that many rooks were killed for their livers to cure the rickets, and Whistler praises the livers of cows and frogs). The divine Fuller's mention of the woman of the West who healed many by cauterizing the vein behind the ear, to which attention is drawn by Mr. Poynter, seems to be a layman's ignorant statement concerning the common treatment by English nurses of blood-letting by cutting the veins at the back of the ear; this practice is described in detail by Whistler, writing two years earlier.—I am, etc.,

Oxford. H. M. SINCLAIR.

Dr. Ricketts

SIR,—Mr. F. N. L. Poynter (May 12, p. 1081) is mistaken in his suggestion that Fuller's reference to rickets in *Good Thoughts in Worse Times* has not been noted by the historians. In the excellent section "Rickets in England" in *The Englishman's Food*, Drummond and Wilbraham, 1939, the early references, including Fuller's, are dealt with at some length.

There is, however, an earlier English reference than Fuller's which I have not seen noted elsewhere. On p. 980 of the monumental *Theatrum Botanicum*, 1640, when discussing the virtues of "The *French* supposed white Thistle," Parkinson writes: "Galen saith that the roote and leaves hereof are of an heating qualitie, and good for such persons that have their bodies drawen together by some Spasme or Convulsion, or by some other infirmitie, which disease is truely to be called the Rickets, which happening sometimes to children doth so binde them in their Nerves, Ligaments and whole structure of their body, that it suffereth them not to grow or prosper eyther in height strength or alacritie." This is not a very detailed description, but it is an obvious reference to the condition which by then had come to be recognized as a distinct disease, and may be the first in an English medical book.

With regard to the first record of the English word "rickets," the earliest appearance found by Drummond and Wilbraham was in a Bill of Mortality for the City of London dated 1634, which recorded 14 deaths from that cause.

The same authors point out that the early references to rickets all indicate that it first attracted attention about 1620. This is further supported by an interesting note by that garrulous antiquary John Aubrey, which was first brought to light by Oliver Lawson Dick in his edition of the *Brief Lives*, 1949, and which certainly bears repetition in a medical journal: "I will whilst 'tis in my mind insert this Remarque, viz.—about 1620 one Ricketts of Newberye, a Practitioner in Physick, was excellent at the Curing Children with swoln heads, and small legges: and the Disease being new, and without a name, He being so famous for the cure of it, they called the Disease the Ricketts: as the King's Evill from the King's cureing of it with his Touch; and now 'tis good sport to see how they vex their Lexicons, and fetch it from the Greek Ραχις, the back bone."

I think this derivation is as likely as any, and it would be interesting to know more about "Dr. Ricketts, of Newberye."—I am, etc.,

Friern Barnet, N.11. G. O. MITCHELL.

Herpes Zoster and Chloramphenicol

SIR,—We wish to report the following case.

A woman aged 45 years was seized with some discomfort in the left eye on November 10, 1950. The pain increased in severity, radiating up to the forehead, and was accompanied by some photophobia and epiphora. Two days later she sent for her doctor (R. G. K. H.), who found the eye in an inflamed condition and asked an ophthalmologist (J. A. R.) for a second opinion.

Examination disclosed only a mild generalized conjunctival suffusion with a localized patch of definite conjunctival injection at the limbus at 4 o'clock. It was thought likely that a keratitis or possibly an iritis would develop. Suitable local treatment for a conjunctivitis was instituted without benefit, and every effort to allay the pain by analgesics, including morphine, was tried without much avail.

On the morning of November 14 a small erythematous patch appeared on the forehead on the course of the supraorbital nerve and the eyelids had become swollen. There was increased conjunctival injection. A diagnosis of herpes zoster of the supraorbital branch of the left trigeminal nerve was made by R. G. K. H. Later in the day she was seen by all three of us, when she was becoming worn out with intense pain in the eye and the lack of sleep. The diagnosis of herpes zoster was now quite definite, as the patch on the forehead had a number of small vesicles on it and there was one spot at the paranasal site in the distribution of the nasociliary nerve. The eyelids were swollen and there was some conjunctival injection, but the cornea was clear. The patient was started on 0.5 g. chloramphenicol six-hourly the following day, with 1% atropine drops daily to the eye. In two days she was free from pain, while the herpetiform eruption and congestion of the eye were subsiding. The drug was continued in smaller doses for a further three days and the atropine discontinued.

When she was last seen five weeks from the onset the neuralgic pains were considerably less and she was getting about the house quite well. There was some residual swelling in the upper eyelid with a little conjunctival injection and one minute corneal infiltrate paracentrally at 9 o'clock.

In view of the annotation "Herpes Zoster and the New Antibiotics" (*British Medical Journal*, 1950, **2**, 1485) there are several points about this case which are worth considering. Chloramphenicol was given early, and produced rapid relief from pain and rapid recession of vesiculation and oedema. There was definite evidence of corneal involvement, but this did not progress. This is all completely contrary to the normal experience in a case of this type.

Further, the husband, a friend, and the cook all developed chicken-pox about a fortnight after the onset of the patient's herpes zoster. This would seem to establish the fact that the virus concerned was of the same strain as that in chicken-pox, and presumably explains the efficacy of chloramphenicol in this particular case.

One of us has long held the view that there is more than one type of infection responsible in herpes zoster to account for the undoubted association of one group of cases with outbreaks of chicken-pox and the absence of this association in the remainder. This would also explain the varied results accompanying the use of chloramphenicol in cases of herpes zoster.—We are, etc.,

Winchester.

R. G. K. HODGSON.
J. A. ROBERTSON.
C. B. S. FULLER.

SIR,—Dr. A. Barham Carter's excellent paper (May 5, p. 987) has inspired us to write of our own experiences in six cases in general practice—a much smaller number than his experiences cover—but we think possibly seen even earlier in the course of the disease than his.

Our experiences have been almost identical with his, the early crusting of the lesions being particularly noticeable. They were similar regarding the duration of the after-pain, which did not seem to be at all diminished by the use of the antibiotic drugs. All our cases were in old people.

At the moment, it seems to us that the large expenditure on antibiotics is unwarranted in cases of zoster while the prices remain at a high level, and we have discontinued the use of them for this reason, although the case against is by no means proved.—We are, etc.,

Norwich.

F. R. WILSON.
P. H. A. JONASON.

Tests for Sugar During Antibiotic Treatment

SIR,—Because streptomycin and dihydrostreptomycin are reducing agents and contain sugar in their molecular structures, routine reduction tests performed on the urine from patients receiving intramuscular injections of these antibiotics may be positive. Also it has been recorded recently that similar results are encountered when massive intravenous penicillin is given—e.g., 86 million units average daily dose (Whipple and Bloom, *J. Lab. clin. Med.*, 1950, **36**, 635).

Recently in this laboratory repeated examinations on cerebrospinal fluids obtained from a patient with *Staphylococcus aureus* meningitis were made. Apart from other findings, the sugar estimations during a course of chloramphenicol showed a sugar decline from 80 mg.% to 33 mg.% over nine days. On the twelfth day the C.S.F. sugar was again 33 mg.%. It was decided to change the treatment, and 100 mg. dihydrostreptomycin sulphate in 10 ml. distilled water was given by intrathecal injection. Twenty-four hours later a sugar content of 55 mg.% in the C.S.F. was recorded.

In both tubercular and pyogenic meningitis considerable attention is given to the C.S.F. sugar content by most authorities, and the raising of the total amount of reducing substances in the C.S.F. by intrathecal injection of antibiotics may give temporary false sugar values, with no accurate index for correction available, so that estimations carried out during and for an indeterminate time after this form of treatment are invalidated.—I am, etc.,

Board of Health Laboratory,
Guernsey.

HENRY WILSON,
Technician in charge.

Warts

SIR,—I have read with considerable interest the paper by Drs. A. Lyell and J. A. R. Miles, together with the annotations on the fascinating subject of warts (April 28, pp. 933–4). A study of this common affection makes one realize some of the limitations of medical knowledge and teaches, above all, humility. One of the most simple and banal of conditions, the wart would seem to obey no laws other than its own. Apparently a virus infection, it comes and goes as it pleases. Recurrences are common after surgical removal and yet quite frequently lesions disappear as a result of wart charming. The exact significance of inclusion bodies, demonstrable in only a small percentage of warts, has for long been a vexed question, although they are generally accepted as evidence of a virus aetiology. The fact that Lyell and Miles were able to show that these bodies occurred predominantly in plantar, palmar, and peri-ungual warts is of considerable interest and merits further investigation, but unfortunately the series of cases is small, and where one is dealing with so ubiquitous a subject one must have a very large number of cases to justify drawing clinical conclusions. This particularly applies to the suggested resuscitation of the word myrmecia. From the point of view of wart charming, it may be of use, but from a scientific point of view it can but add confusion to a subject already confused enough. Indeed, I think the same argument applies to the word verruca, so beloved of the chiropodist, and would suggest that it should give way entirely to that simple but expressive word "wart."

While agreeing with your annotator that as regards immediate results surgical removal is the most reliable method of treatment, I feel that the high relapse rate is not emphasized enough. When this is taken into account the long-term result varies but little from that of the more simple and practicable methods, the majority of which act in all probability by "charming." It would seem reasonable to suggest that the individual practitioner should take advantage of this susceptibility in the wart, and, if his scientific conscience will not allow of the more bizarre and dramatic forms of wart charming, that he should at least try the effect of suggestion in the form of simple drying pastes and lotions. By so doing he will find that he will reduce, frequently to an unexpected degree, the number of lesions requiring surgical removal. In particular the usefulness of 3% formalin in treatment of plantar warts is not always appreciated, for its routine use will usually serve to clear 50–70% of these lesions.—I am, etc.,

Huddersfield.

A. J. E. BARLOW.

Serum Enzyme Levels in Perforated Ulcer

SIR,—Dr. H. Wapshaw in his paper (May 5, p. 995) has not discussed one possible mechanism which could elevate the levels of serum amylase and lipase in cases of perforated peptic ulcer. The findings reported could be caused by spasm of the sphincter of Oddi, which in turn would lead to increased pressure in the duct system of the pancreas and consequent absorption of the enzymes into the portal venous tract. Though this spasm would be produced reflexly, the use of opium derivatives or pethidine to relieve pain might be a potent determining factor.

This hypothesis would not only account for the findings noted in these cases but also in those other acute upper abdominal conditions—small-gut obstruction and peritonitis—in which raised serum enzyme levels have been reported. Absorption of enzymes from the peritoneal cavity cannot arise in those lesions. This explanation is in keeping with the recent experimental work reported in cases of biliary dyskinesia in man by J. B. Gross, M. W. Comfort, D. R. Mathieson, and M. H. Power (*Proc. Mayo Clin.*, 1951, **26**, 81), who observed elevation of the serum amylase and lipase in a few individuals to whom codeine had been given, and with the occasional finding of raised enzyme levels in the blood of patients with stones in the gall-bladder, in whom no manifest signs of pancreatitis are found at operation.

Support for the validity of this contention could be easily obtained. In these patients a fall in serum enzyme values should follow the administration of nitrites, which relax the sphincter of Oddi.—I am, etc.,

Manchester. HENRY T. HOWAT

Expectant Treatment of Perforated Ulcer

SIR,—I read with considerable interest Mr. A. Davis Beattie's review of the expectant treatment of perforated peptic ulcer in 40 unselected cases (May 5, p. 992). As a hitherto confirmed laparotomist I was very impressed by his figures and was therefore the more surprised to read that "as a result of his experiences" Mr. Beattie has abandoned expectant treatment. It seems to me that he is too severe on himself. Analysis of the four fatal cases shows that one patient never sufficiently recovered from the initial shock to have the laparotomy awaiting him, one had acute heart failure on admission and could not have stood laparotomy anyhow, and one, an elderly woman, died 72 hours after delayed laparotomy from "peripheral failure." Would these three patients have fared any better had they been admitted under a laparotomist? Only the fourth might reasonably have been saved by early operation, and who knows what operative or post-operative misfortune might have occurred among the 36 who survived?

It is interesting to note that three out of the four patients who died were over 50 years of age, while the fourth (aged 46) would have been lost to anyone. Further, the only young patient (36) submitted to operation after expectant treatment, and found, moreover, to be suffering from the particularly lethal anterior gastric perforation, survived.

It seems to me, therefore, that the most equable conclusion to be drawn from this series, admittedly small, is that it is reasonably safe to employ expectant measures on patients under the age of, say, 50, while, on account of the greater risk of intercurrent weakness and failure to stand the strain, early operation is preferable in the older age groups.—I am, etc.,

Darlington. B. B. FRESHWATER.

Allergic Encephalomyelitis

SIR,—I ask the favour of space to take issue publicly with the author of your leading article on this subject (May 5, p. 1002). In reference to my work on the subject he writes: "Lumsden found non-myelinated (foetal) nervous tissue fully encephalitogenic." This statement is an unjustified interpretation of my findings (*Brain*, 1949, **72**, 517) from which I reported that "brain tissue from nearly full-term guinea-pig foetuses is highly encephalitogenic." I did not make, and was not in a position to make, any statement about the degree of myalin formation already in progress in these brains. My empirical findings with foetal guinea-pig brain appeared worthy of record, however, in view of the report of Kabat and his colleagues (*J. exp. med.*, 1948, **88**, 417) that the encephalitogenic factor did not appear in the rabbit's cerebrum until about the 12th day of post-uterine life. Kabat and his colleagues added, "In this respect it parallels the laying down of myelin."

It should be noted, however, as pointed out in my paper, that whole brains from foetal guinea-pigs were used. As such, the specimens included material from cerebellum and brain-stem as well as cerebrum. From the analogy of human myelinogenesis, as studied in the classical work of Flechsig and more recently by Lucas Keene and Hewer, it is possible that myelination is already in progress by the 60th day of intrauterine life in the guinea-pig. Though work has been done on myelination in the rat brain (Gonzalez, *J. comp. Neurol.*, 1929, **48**, 459) no systematic work has yet been done in this field in the case of the guinea-pig so far as I have been able to learn.

Far from disagreeing with the observations of Kabat and his colleagues, I am inclined to believe that the appearance of the encephalitogenic factor has something to do with the development of the myelin, and at the time of the experiments reported I suspected that the apparently greater activity of brain tissue from near-term guinea-pig foetuses might have something to do with greater activity in elaboration of myelin or with co-existent greater oligodendroglial activity at this stage.

Since the brains of smaller mammals are not very suitable for study of the relationship of the encephalitogenic factor to myelination some further studies have been begun using foetal human brain from cases of abortion or miscarriage. To date it has been found that, while adult human brain contains the factor, three-month foetal brain does not.—I am, etc.,

Aberdeen. C. E. LUMSDEN.

Who Shall Decide Treatment?

SIR,—Your anonymous obstetrical correspondent (May 12, p. 1083) makes the statement that the Central Midwives Board shows "a complete lack of comprehension of the circumstances as they are at present." In point of fact the reverse is clearly true. They comprehend that women are leaving maternity hospitals before the tenth day and they do not like it. But nowhere does your anonymous correspondent show any appreciation of why the woman comes into hospital: it is not in order that she shall go out as soon as possible, but that she shall go home with a live baby firmly established at the breast. The issue is between quality and quantity, and however much the standard of obstetrics in hospitals is lowered in the interests of a greater intake, there will still remain many to have their babies peacefully at home with the midwife. So why lower it at all? The answer to how long a woman should stay in hospital is until breast-feeding is firmly established, and it is certainly not less than ten days.—I am, etc.,

Blackheath, S.E.3. KEITH VARTAN.

Polymastia and Lactation

SIR,—I was particularly interested in Mr. Hamilton Leckie's article (May 12, p. 1060) on a case of polymastia, because in the issue for March 3, 1928 (p. 346), I reported an exactly similar case. Again, in the *Journal* of March 14, 1936 (p. 556), I wrote another letter in reply to Mr. R. Graham-Campbell, of Bath, who reported (March 7, 1936, p. 471) a case of polythelia having ten nipples, and possibly an eleventh, together with the most convincing photograph I have ever seen of the condition. I made at that time some observations anent the position of accessory breasts and nipples, and expressed the opinion that they always occurred in the "mammary line," or "mammary ridge" as Mr. Leckie terms it, and never elsewhere such as the back, shoulders,

buttocks, or outer side of the thigh, as stated by some authorities, and Mr. Leckie rightly stresses the same point.

My patient suckled her infant successfully from the two normal breasts, the accessory ones giving little trouble except at first. But I delivered her in her own home, where she escaped the embarrassment which the morbid curiosity of neighbours in a hospital ward might have caused her. It seems a pity to stop breast-feeding just because an extra nipple makes one wet for a few minutes. Moreover, these supernumerary mammae, being as a rule entirely separate entities unconnected with the main organs, tend to dry up if not used for suckling, even though the main organs are actively used for their proper purpose. However, it is admittedly a much more valid excuse for bottle-feeding than most reasons proffered by the mothers of to-day, who appear almost universally opposed to feeding their young by the means Nature provided.—I am, etc.,

Penzance. G. B. RICHARDSON.

Preventing Ether Explosion

SIR,—In the *Journal* of May 12 (p. 1087) is an article "An Unusual Ether Explosion." I made it quite clear in a paper which I read to the Royal Society of Medicine in 1934, on my own experience of an explosion, that 95% oxygen and 5% ether is a most dangerous mixture, but I also stated that such explosions could be avoided by flooding the anaesthetic apparatus with CO_2, if ether has been used or if there is any danger of ether vapour being left in the apparatus.

Ether vapour may travel from bottles insecurely corked or stoppered as far as five yards away from a flame or sparks from an electric cautery, and a simple method of flooding the apparatus with CO_2 should be appreciated where there is any chance of danger.—I am, etc.,

London, S.W.1. R. W. IRONSIDE.

POINTS FROM LETTERS

Premenstrual Tension State

Dr. P. D. MULKERN (Bristol) writes: This condition (May 12, p. 1068) is frequently met with in general practice and I have adopted the hypothesis that excess oestrin is present. The condition responds well to androgens given parenterally or orally, but often relapses after a few months. In these patients it would appear that the pituitary–ovarian complex has a low threshold for emotional and psychic impulse arriving via the hypothalamic area. I also recognize a menopausal hyperoestrinization syndrome expressed by increasing periods of amenorrhoea followed by heavy bleedings, hypertension, tachycardia, headaches, erythema of the neck and sternum, fullness of the lower abdomen, urinary frequency, and obesity of grossly female type. This responds well to a three-months course of androgens and does not relapse so frequently. Multiple uterine fibroids are so often found in females bearing this temperament that I often speculate on the possible role of oestrogen excess in the causation of fibroids.

Who Shall Decide Treatment?

Dr. J. NOEL JACKSON (Rawtenstall) writes: In my view the Central Midwives Board is merely fulfilling its proper function when it takes a stand on a matter of principle. The circular presumably means what it says—namely, that it regards discharge before the tenth day as undesirable. An obstetrician working almost exclusively in a hospital sees only one side of the picture. Some of us have seen rather more of the drawbacks of domiciliary midwifery at first hand. The conditions which impel the hospital obstetrician to clear his beds early are related to shortage of nurses and accommodation. These very conditions result from modern circumstances which the patient feels most acutely on return home, and this is an argument for later, not earlier, discharge, but the hospital obstetrician may not have daily reminders of this.

Arm Girth and Blood Pressure Readings

Dr. A. D. MCLAUGHLIN (Ilford) writes: A useful tip that I have picked up to solve the problem of the small cuff and the bulky limb (April 14, p. 832) is the firm application of an ordinary 6 in. (15 cm.) bandage over the cuff. This gives fairly accurate readings and overcomes the unsightly bulging of the corseted rubber bag.

Obituary

SIR BASIL HALL, K.C.B., O.B.E., M.R.C.S.
(Surgeon Vice-Admiral, R.N.)

Surgeon Vice-Admiral Sir Basil Hall, who died at Haslemere, Surrey, on May 16, served in the Royal Navy for thirty-seven years and was Medical Director-General of the Navy and an Honorary Physician to the King from 1934 to 1937. He was 75 years of age.

Robert William Basil Hall was born at Southsea in 1876 and educated at Portsmouth Grammar School. He studied medicine at Guy's Hospital, qualifying in 1900. In the same year he entered the Royal Navy as a surgeon and steadily progressed to the top of his chosen branch of the profession, being promoted to staff surgeon in 1908, surgeon commander in 1916, surgeon captain in 1925, surgeon rear-admiral in 1925, and surgeon vice-admiral in 1934. In 1913, while serving in H.M.S. *Active*, he received the thanks of the Scottish Office for valuable service rendered at St. Kilda, where the bulk of the population was suffering from influenza and in a deplorable condition. During the first world war he served in the cruiser *Lowestoft*, which took part in the Dogger Bank action and other operations in the North Sea, and in 1917 was appointed senior medical officer of the submarine service. He took a great interest in the special problems arising in underwater craft, and his *Handbook for Medical Officers of the Submarine Service* was published in 1920 and became a standard book of reference.

From 1920 to 1926 he served as an assistant to the Medical Director-General and then until 1929 as Deputy Medical Director-General. In 1930 he was appointed as medical officer-in-charge of R.N. Hospital, Plymouth, and during the three years in which he held this post he was responsible for many valuable improvements in the hospital organization. In 1934 he became the Medical Director-General of the Navy. He retired from the Navy in 1937, and during the last war he performed useful work as chairman of the National Service Medical Board at Guildford. For a short time after the first world war he served on the Naval Medical Service Subcommittee of the B.M.A.

During the course of his successful career Hall was made an O.B.E. in 1924, a C.B. in 1930, and a K.C.B. in 1936. In 1922 he was awarded the Gilbert Blane Medal by special adjudication for conspicuous zeal and professional ability displayed throughout his Service career. In 1920 he was made an Officer of the Order of the Redeemer (Greece) and in 1937 a Commander of the Venerable Order of St. John of Jerusalem.

Sir Basil Hall was twice married. His first wife died in 1948, and in 1950 he married Dorothy, daughter of the Rev. Charles Hemsley and widow of Rear-Admiral Cyril Copner.

J. R. C. GREENLEES, D.S.O., M.B.

Dr. J. R. C. Greenlees, who had a distinguished career first as a physician and then as headmaster of Loretto School, died in Edinburgh on May 16, aged 72.

James Robertson Campbell Greenlees was born in Glasgow in 1878. He was educated at Kelvinside Academy; Loretto School; St. John's College, Cambridge; and Glasgow University. One of the foremost rugby footballers of his day, he played for Scotland in

many games. After graduating B.Chir. in 1905 and M.B. in 1907 he was elected to the out-patient staff of the Western Infirmary, Glasgow, and in 1908 he became assistant physician at the Royal Hospital for Sick Children. He served with great distinction during the first world war, becoming an acting lieutenant-colonel commanding the 98th Field Ambulance in 1916. He was awarded the D.S.O. and Bar, the Legion of Honour, and mentioned four times in dispatches. At the end of the war he returned to his medical work in Glasgow, and his appointment to the headmastership of Loretto in 1926 came as a surprise. But he was a great success as an educationist, and no doubt his wide experience in paediatrics gave him an unusually deep understanding of young people's needs. Under his headmastership Loretto flourished, and the numbers of boys became greater than ever before. Although he intended to retire in 1940, he retained the headmastership of the school until the end of the last war.

Although Greenlees gave up the practice of medicine when he took the headmastership of Loretto he did not lose interest in his old profession, and in 1947 he was appointed chairman of the South-Eastern Regional Hospital Board in Scotland, a position he held almost until his death. In 1948 he was honoured by being appointed surgeon to the King's Bodyguard for Scotland, the Royal Company of Archers. He married in 1922 Allison Hope, daughter of Sir John Cargill. They had one son and one daughter.

F. H. EDWARDS, F.R.C.S.Ed.

The St. John Ambulance Brigade has suffered a great loss by the sudden death at Harrogate, on April 29, of its Surgeon-in-Chief, Mr. F. H. Edwards, at the age of 55.

Francis Henry Edwards studied medicine at the University of Liverpool, qualifying in 1920 and graduating M.B., Ch.B. a year later. He had a distinguished academic career, at one time holding a Holt fellowship in physiology. In 1925 he became a Fellow of the Royal College of Surgeons of Edinburgh. After holding resident appointments at the Children's Infirmary, Liverpool, and the Royal Salop Infirmary he eventually settled down in Shrewsbury, where he was one of that great band of general-practitioner consultants who were such pillars of strength in the smaller provincial towns. In September, 1948, he relinquished general practice to devote himself entirely to gynaecology and obstetrics. He was consultant obstetrician to the Royal Salop Infirmary and to the counties of Shropshire and Montgomeryshire, and he was also gynaecological surgeon to the Wellington Cottage Hospital. His enthusiasm for his professional work was as abundant and fresh as that of the student becoming aware of the wonders of medicine for the first time. His social activities were widespread, and it was remarkable that one man could have packed so much goodness into such a short span of life. To the St. John Ambulance Brigade he dedicated the whole of his personal life. After being surgeon to the Shrewsbury nursing divisions and corps surgeon he became county surgeon in 1936 and county commissioner in 1947. He had held the distinguished position of Surgeon-in-Chief to the Brigade only since January of this year, having previously been deputy Surgeon-in-Chief, but in the short space of time he had held this office his ability, enthusiasm, industry, and personality made a profound and lasting impression on the great movement he served. He was recently appointed a Commander of the Order of St. John of Jerusalem. The large and representative assembly at his memorial service bore testimony to the deep regard and affection in which he was held by all. He leaves a widow and two sons, both of whom are in the Services.—M. M. S.

PETER BULL, M.D., Hon. F.R.C.S.

Professor Peter Bull, who died on January 31 at the age of 81, was for many years the most forceful personality of the surgical world in the Scandinavian countries. Quite early in his career his work for four years at the Pathological–Anatomical Institute of the Rikshospital in Oslo left a permanent impression on his outlook as a surgeon. In 1912 he was appointed professor of surgery at the University of Oslo, and during the next 16 years so much of his time was absorbed by his successful activities as a teacher and examiner that he resigned the chair of surgery at an early date in order to devote more time to research and clinical work. As early as 1908 he set himself the uphill task of teaching his more conservatively minded colleagues the imperative necessity for early operation in appendicitis. The many and quite temperamental debates on this subject gave ample opportunities for the exercise of a logical mind and a witty tongue expressing the thoughts of a clinician trained to think in terms of morbid anatomy. As early as 1914 Bull performed his first thoracoplastic operation. Thenceforth he contributed much original work on this subject, and his reputation in connexion with it was such that on the invitation of the British Medical Association he delivered a lecture in 1922 at Glasgow on extrapleural thoracoplasty for pulmonary tuberculosis. The following year he gave an address on the same subject at a meeting of the Royal Society of Medicine in London. He was an honorary member of many medical societies abroad, and he much appreciated his honorary membership of the Association of Surgeons of Great Britain and Ireland and fellowship of the Royal College of Surgeons of England.

Dr. ALEXANDER BROWNLEE, for many years medical superintendent of Glan Ely Hospital for Tuberculosis, died at Cardiff on May 9 at the age of 76. The son of Mr. Alex Brownlee, of Edinburgh, he qualified as a dentist before taking the Scottish triple qualification in 1901. In later years he graduated M.D. at Durham, became a member of the Royal College of Surgeons of Edinburgh, and took the D.P.H. of Cambridge University. After serving as a house-surgeon at Ingham Infirmary, South Shields, he came to Cardiff in the early nineteen hundreds as a house-surgeon at the Cardiff Infirmary, and while there he specialized in anaesthetics. For some years he practised in Cardiff as an anaesthetist, but in 1914 he was appointed medical superintendent of Glan Ely Hospital, Cardiff, which had been opened shortly before as a hospital under the King Edward VII Welsh National Memorial Association for the treatment of tuberculosis, both pulmonary and non-pulmonary. He remained at this post until his retirement in 1943. He became an expert in the diagnosis and treatment of non-pulmonary tuberculosis and was a very capable surgeon. He was extremely interested in the "light" treatment of lupus and of surgical tuberculosis in children and superintended the building and equipment of a large light department in the hospital. He was in charge of aftercare clinics for non-pulmonary tuberculosis in South Wales and was also a clinical teacher in tuberculosis at the Welsh National School of Medicine. He had been, in addition, president of the Cardiff Medical Society and vice-president of the Section of Tuberculosis at the B.M.A. Annual Meeting in 1928. In

later life he became interested in law and was called to the Bar at Gray's Inn in 1940.

Dr. Brownlee never enjoyed good health and in his latter years had had considerable difficulty with his sight, but despite this he was greatly interested in Association football and had been a director of the Cardiff City Football Club for forty years, having been at one time the chairman of directors and medical officer to the club. He was the author of papers on "Administering Ether" and "Congenital Absence of Head of Femur." His widow and a daughter survive him.—J. K. D.

Dr. LENNARD CUTLER died on May 15 at a nursing-home in London at the age of 86. After studying medicine at St. George's Hospital Medical School, he qualified as L.S.A. in 1889 and became M.R.C.S., L.R.C.P. in 1891. He had a very thorough preparation for general practice as house-surgeon, house-physician, resident obstetric officer, and assistant surgical registrar at St. George's, and as house-physician and physician to out-patients at the General Lying-in Hospital. After that he joined as junior partner the late Dr. Ewart, brother of the late Dr. William Ewart, the eccentric senior physician at St. George's Hospital in the late Victorian era. The firm of Ewart and Cutler was a very well known one in South Kensington in the heyday of that once aristocratic locality, and its prosperity was based on the real efficiency of both partners. Cutler lived for a great number of years at a corner house of somewhat unusual and striking design, No. 1, Kensington Gate. He continued in practice until a comparatively recent date, though latterly he would see only a few old patients who were dismayed at the idea of having to find a new attendant. He was, of course, already about 50 when the first world war began, and in consequence did not attempt any military service. As an all-round practitioner of a type now becoming increasingly rare, he worthily represented what is now almost a tradition; and the profession is the poorer for his loss.

Medico-Legal

DEATH AFTER OVERDOSE OF PARALDEHYDE

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

The danger and possibility of confusion inherent in the Latin symbols used in prescriptions were commented on by the Belfast City coroner at a recent inquest on a 72-year-old woman who died after an overdose of paraldehyde.

The patient had been admitted to hospital for a palliative operation on a large arteriovenous aneurysm involving the vessels at the back of the skull and brain. She had consented to undergo the operation only on condition of having a general anaesthetic, and 6 drachms (21 ml.) of paraldehyde with 6 drachms of olive oil were prescribed as premedication to be followed by 1/100 gr. (0.65 mg.) of atropine, subject to her weight not being less than 8 stone (50.4 kg.).

When the patient was weighed it was reported that her weight was 9 stone 10 lb. (61.2 kg.), and the resident medical officer decided that the premedication should be increased from 6 to 8 drachms (28 ml.) of paraldehyde and the same of olive oil. When he came to alter the entry on the list of patients who were to receive premedication for operation next morning, besides altering the figures he inadvertently altered the symbols from drachms to ounces.

The staff nurse in charge of the patient thought the dose of paraldehyde unusually large, but on checking with the entry in the list concluded from the alteration of both figures and symbols that the premedication had been deliberately increased. The paraldehyde and olive oil were accordingly administered per rectum at 9 a.m., and about half the dose was retained.

When the operation was started at 10 a.m. it was noticed that the patient was deeply sedated, though her general condition was otherwise satisfactory. But after some time the surgeon and the anaesthetist became worried about her respiration, and discovered that an overdose of paraldehyde had been administered. Remedial measures were taken and the operation was ended as soon as possible. During the day the patient's condition improved and next morning her respiration was good and her general condition fairly satisfactory. Later her condition deteriorated, and she died suddenly at about 4.30 a.m. the next day.

At necropsy it was found that her lungs were oedematous, with areas of marked congestion on section. There was extensive oedema of the air spaces and well-established pneumonic inflammation throughout. There was also acute inflammation of the lining of the trachea. There was no evidence of degeneration due to any poison or toxin, and the pathologist's opinion was that death was due to pneumonia superimposed on oedema of the lung.

The coroner recorded the verdict that the patient died from pneumonia following oedema of the lungs, possibly caused by a toxic dose of paraldehyde accidentally prescribed. He exonerated from all blame the nurse who had administered the premedication.

The Services

The *London Gazette* has announced the award of the George Medal to Acting Squadron Leader THOMAS COLIN LYALL BROWN, M.B., B.S., R.A.F. Station, Abingdon. The citation reads as follows:

"Squadron Leader BROWN is Senior Medical Officer at Royal Air Force Station, Abingdon. On the night of December 20, 1950, he was travelling as a passenger on a Route Flying Fatigue trial from Singapore, for Headquarters, Transport Command. During the flight, a propeller blade broke loose from one of the engines of the Hastings aircraft in which Squadron Leader BROWN was a passenger. The blade cut through the fuselage and seriously injured the co-pilot, who was lying on the bunk in the crew's compartment. It also severed the control cables to the rudder and elevators. Within a few seconds the faulty engine fell out of the aircraft. Squadron Leader BROWN immediately went to the aid of the injured co-pilot and gave him medical attention. Although he fully appreciated the danger involved, he continued to administer medical attention until the aircraft crashed. When all others were at crash stations he remained at his post with the injured man. If he had been prepared to leave him, he could have taken up a position in the passenger cabin on one of the stressed, backward facing seats, all of whose occupants escaped serious injury. The crash took place at Benina, killing five members of the crew, including the injured co-pilot. Squadron Leader BROWN was himself seriously injured, and there is no doubt that he consciously risked his life in order to save that of the injured officer. He carried out his duties in accordance with the traditions of his profession without regard for his own personal safety. He has set an outstanding example at all times and has completed eighty parachute descents from balloons and aircraft in the course of his duties with the Parachute School."

Surgeon Lieutenant-Commanders G. L. Ward, D.S.C., H. A. Mogg, T. T. Hardy, T. M. McEwan, D. H. Anderson, C. S. Cane, J. B. W. Hayward, and G. A. Hart, R.N.V.R., have been awarded the R.N.V.R. decoration.

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on May 15 a Readership in Human Nutrition was established and Dr. H. M. Sinclair, Director of the Laboratory of Human Nutrition, was appointed to the post for seven years from October 1.

A bequest to the University has been made by the late Miss Mary Goodger for the establishment of scholarships in memory of her father and herself. It was decided in Congregation on May 15 that there shall be two Mary Goodger Scholarships and one Henry Goodger Scholarship to assist research into the causes and prevention of disease, with special reference to the study of disease in its early stages; that one scholarship shall be awarded annually and one scholarship awarded in one year out of three shall be a Henry Goodger Scholarship; that the scholarships shall be open to all members of the University provided that in the award of the Mary Goodger Scholarship preference shall be given to women; and that the scholarships shall each be tenable for two years but may be extended for a further year. The annual emoluments of each scholar shall be not less than £300 or more than £400. Full particulars of the scholarships may be obtained from the Regius Professor of Medicine.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending May 5 (No. 18).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending May 5					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	45	2	4	2	2	41	2	17	5	2	703	367	41
Deaths	—	—	—	—	—	—	—	1	—	—			
Dysentery	833	145	114	10	1	341	6	89	—	1	469	193	59
Deaths		—		—			—		—				
Encephalitis, acute	2	—	1	—		2	1	—	—	—	7	2	—
Deaths		—			—		—						
Erysipelas			13	1	6			20	5	6			
Food-poisoning	130	16		2		56	4		2				
Infective enteritis or diarrhoea under 2 years				9	16					17			
Deaths	10		1	2	—	18		3	—	1			
Measles*	18,310	871	540	233	144	6,317	141	467	238	147	13,139	8,442	2,035
Deaths		1	1	—	—			—	—	1			
Meningococcal infection	27	3	14	1	4	34	5	18	2	2	149	52	21
Deaths		1	—				—	1					
Ophthalmia neonatorum	33	1	8	1		29	3	7	—		101	87	29
Pneumonia, influenzal	588	36	5	7	1	534	20	6	7	—	1,096	534	494
Deaths (from influenza)†	10	5	—	—	2	24	6	1	1	4			
Pneumonia, primary			191					156					
Deaths	183	25		8	8	152	17		5	11			
Poliomyelitis, acute:													
Paralytic	17	1	3	1		25	2	—	4	2	25	10	4
Non-paralytic	4	—			—								
Deaths§	1	—				2	—			—			
Puerperal fever			2				—	6					
Puerperal pyrexia‖	81	16	2	—		87	8	11			175	122	87
Scarlet fever	1,032	73	135	28	66	1,267	88	130	71	83	1,646	1,267	873
Deaths		—	—	—	—			—	—	—			
Smallpox	—	—	—	—		3	—	—	—				
Deaths				—					—				
(1) Tuberculosis, respiratory			143	40				169	40				
(2) Tuberculosis, non-respiratory			41	5				47	—				
(1) Deaths	126	17	22	3	14	193	32	36	3	13			
(2) Deaths		2	4	2	6		1	7	—	5			
Typhoid fever	4	—	—	—	—	3	—	1	—	2			
Deaths¶	1	—	—	—		—	—	—	—	—	40	11	2
Paratyphoid fever	7	—	—	1		7	3	—	—				
Whooping-cough	3,483	218	452	61	59	3,229	167	321	49	64	3,299	2,230	1,050
Deaths	4	—	2	—	—	5	1	—	—	2			
Deaths (0–1 year)	237	33	40	10	25	271	36	36	8	29	442	356	258
Deaths (excluding stillbirths)	4,777	748	609	112	173	4,942	715	599	133	230	4,961	4,537	4,229
Annual death rate (per 1,000 persons living)			12·3					12·0					
Live births	7,532	1,277	913	241	508	7,725	1,272	932	230	528	9,570	7,722	6,201
Annual rate per 1,000 persons living			18·4					18·7					
Stillbirths	202	24	20			177	23	22			264	233	179
Rate per 1,000 total births (including stillborn)			21					23					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London, and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

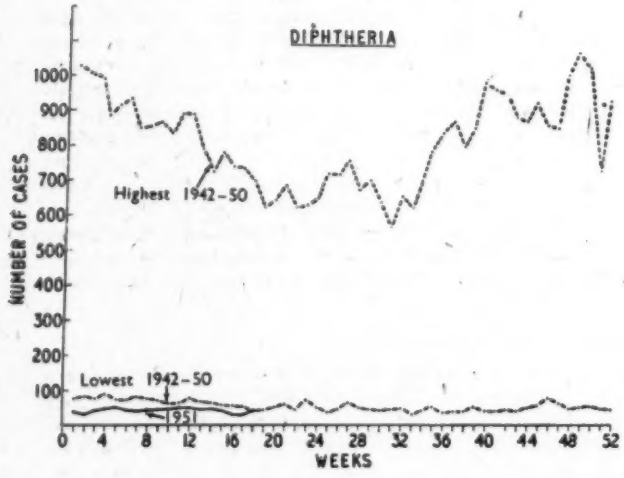
Vital Statistics

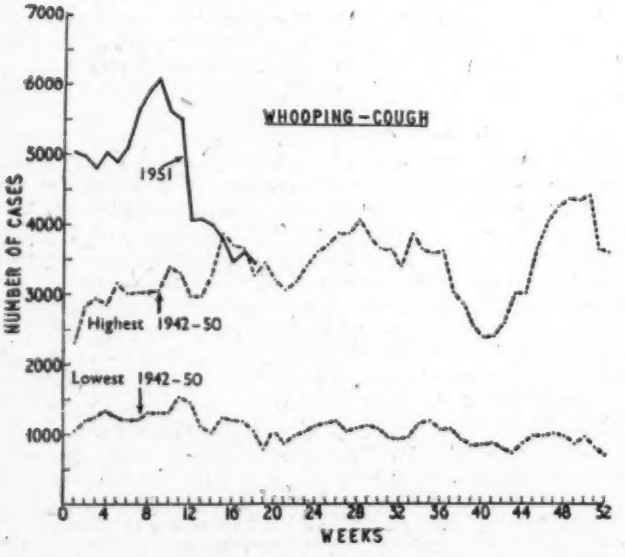
Influenza

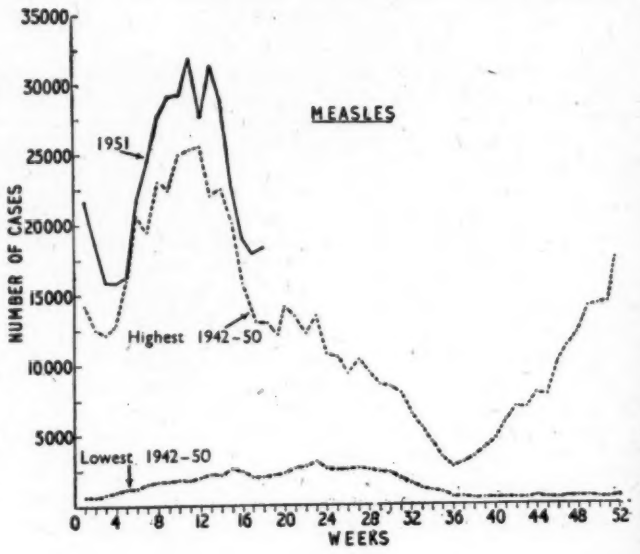
The outbreak of influenza has now subsided to the endemic level. Only 10 deaths were registered in the great towns during the week ending May 5, five of these in London. The recent epidemic was the most severe for several years: 1,269 deaths were registered during the peak week, the largest number for 18 years. The largest of the other peaks during the 18 years were 1,155 in 1937, 1,148 in 1943, and 629 in 1940. During the first 18 weeks of the year deaths from influenza in the great towns numbered 7,278 compared with 1,365 in 1950 and 2,679 in 1949. The curve of mortality during the recent outbreak followed the course of the majority of the epidemics since 1920, rising in the last weeks of the preceding year to a maximum in the early part of the year and then steadily declining.

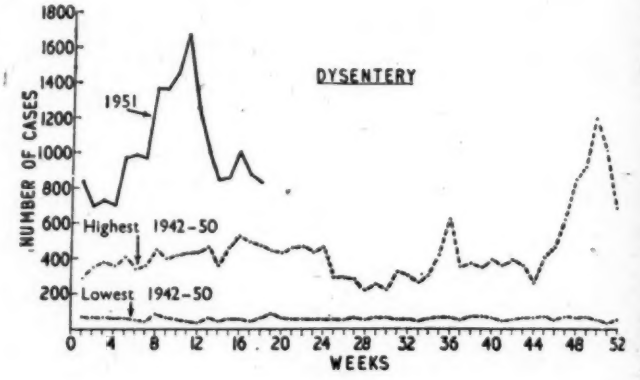
Graphs of Infectious Diseases

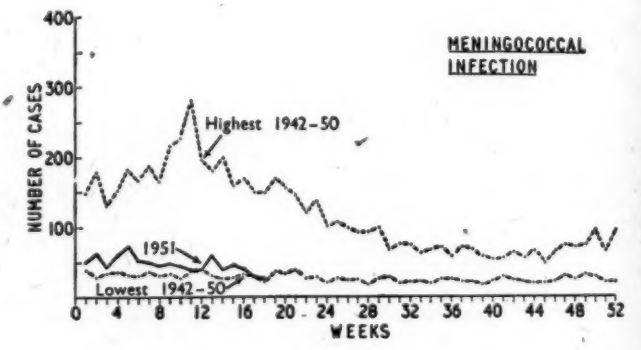
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus - - - - - - -, the figures for 1951 thus ————. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.

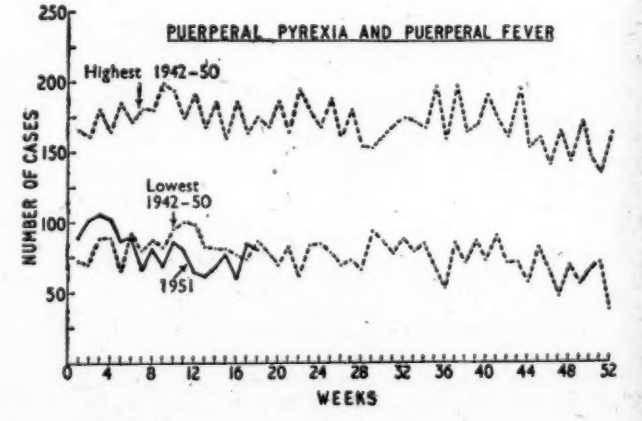












Infectious Diseases

During the week ending May 5 the chief variations in the trends of infectious diseases in England and Wales were decreases in the number of notifications of whooping-cough by 160, scarlet fever by 52, and dysentery by 38, while the only large rise was 304 for measles.

The rapid fall in the incidence of measles has been checked by a rise, but during the preceding four weeks the number of notifications declined by 13,262. Rises in the number of notifications of measles were recorded in many areas. The largest were Durham 160 and Sussex 117. The largest falls were Warwickshire 176, London 146, Surrey 130, and Nottinghamshire 116. Only small variations occurred in the local trends of scarlet fever and whooping-cough. A rise of 13 was recorded in the number of notifications of diphtheria, due mainly to increases in Lancashire 10 and Worcestershire 6. The largest centres of diphtheria were Dudley C.B. 5 and Liverpool C.B. 5. Multiple cases of acute poliomyelitis were reported from Lancashire 3 (Liverpool C.B. 3), Yorkshire West Riding 3 (Leeds C.B. 2), Warwickshire 2, Glamorganshire 2.

The largest of the new outbreaks of dysentery reported during the week were Sussex, Brighton C.B. 28, and Cambridge, Chesterton R.D. 24. The largest returns of dysentery were Lancashire 146 (Bolton C.B. 23), London 145 (Islington 36), Yorkshire West Riding 91 (Bradford C.B. 30), Middlesex 73 (Ealing M.B. 33). The largest outbreak of food-poisoning was in Wiltshire, Malmesbury R.D. 34.

Fewer Immunized Against Diphtheria

The Ministry of Health states that, although diphtheria is being held in check as an epidemic disease, the numbers of babies and children immunized are declining. In England and Wales over 140,000 fewer babies were protected in 1950 than in 1949. Since the immunization campaign began in 1941 over 9,000,000 babies and children have been immunized. Diphtheria deaths have fallen from a pre-war average of 2,800 to 49 (provisional figure) last year—a new low record. Cases during the same period have declined from 55,000 a year to 980 (provisional figure)—also a new low record. The Ministry points out that if diphtheria is to be kept at bay the level of immunization must not be allowed to fall.

Week Ending May 12

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,025, whooping-cough 3,206, diphtheria 38, measles 19,929, acute pneumonia 574, acute poliomyelitis 21, dysentery 940, paratyphoid fever 10, typhoid fever 3. Deaths from influenza in the great towns numbered 15.

Births and Deaths in Mauritius

The estimated population of Mauritius at December 31, 1949, was 456,717. Of these, just over 290,000 were Indians and about 13.000 were Chinese. The birth rate in that year was 46.0 in the total population and 51.0 in the Indian population (the birth rate in England and Wales in that year was 16.9). The crude death rate for the total population was 16.6 and for the Indian population 17.4 (in England and Wales it was 11.8). The infant mortality rate was 91.0 per 1,000 live births in 1949, 181.5 in 1948, and an average of 152.8 in 1939–48 (in England and Wales in 1949 it was 32.37).

The Save the Children Fund has undertaken to train Greek girls as nursery teachers to help Greek efforts to raise the standard of nurseries in their country. The girls will attend a residential nursery training college staffed by British nursery trained personnel under a British director, who will ultimately hand over to the Greeks as soon as they are ready to continue the work.

Medical News

President's Address and Reception

The adjourned Annual General Meeting of the B.M.A., at which Dr. A. W. Sichel, of Capetown, will give his Presidential Address, will be held at 8 p.m. on Friday, June 15, at the Central Hall, Westminster, and will be followed by the President's Reception in the same building. These functions are open to all members and their ladies. Admission will be by ticket obtainable from the Secretary at B.M.A. House. Early application for tickets is advisable. Evening dress with decorations and academic robes should be worn. Academic robes may be hired from Messrs. Ede and Ravenscroft Ltd., 93, Chancery Lane, London, W.C.2.

Changes in the Poisons Rules

The Home Office announces that in Part I of the Poisons List the item "antihistamine substances" is amended to include chlorcyclizine and promethazine, and the following substances are added: gallamine, organic compounds of mercury which contain a methyl (CH_3) group directly linked to the mercury atom, paramethadione. Under Part II of the List the entry "organic compounds of mercury" is amended to read "organic compounds of mercury except compounds which contain a methyl (CH_3) group directly linked to the mercury atom."

Southern Ophthalmological Society

The Society visited the Corneo-Plastic Unit at the Queen Victoria Hospital, East Grinstead, on May 5 for a demonstration by Mr. B. W. Rycroft of the operative technique of lamellar corneal grafting and dacryocystorhinostomy. Cases were also shown illustrating optical, therapeutic, and cosmetic grafts, from which the success of this therapy was apparent. Mr. Rycroft emphasized the urgent need for donor eyes and invited the co-operation of the Society (and of all ophthalmic surgeons) in the provision of donor material. A box for transport of the eye under suitable conditions would be sent in time for any case if a notification were received by the Corneo-Plastic Unit in advance.

French Honour Doctor

Dr. W. S. Parsons, of Mobile, Alabama, who qualified at McGill University in 1917, has been named a Chevalier de la Légion d'Honneur. In a letter to Dr. Parsons the French Ambassador in the United States said that the honour showed the gratitude of the French Government for the services he had rendered to the Allied cause during the two world wars and particularly to the Free French Forces in the East. Dr. Parsons was at one time a temporary surgeon in the R.N.M.S., and lived in China from 1919 to 1942, serving as a major in the Shanghai Volunteers.

Charges for Teeth and Glasses

The charges for National Health Service teeth and glasses came into force on May 21. A full set of dentures will cost £4 5s., one, two, or three teeth £2, four to eight teeth £2 5s., nine or more teeth £2 10s. Glasses will cost £1 a pair, plus the cost of the frames, which range from 3s. 4d. to 15s. 1d. These charges will not apply to the free range of glasses available for children under 16. Those who were already undergoing treatment before May 21 will not have to pay the new charges. The Ministry draws attention to the following points: where a patient prefers to have metal dentures which are not clinically necessary there will be an extra amount to pay; the charge for replacing dentures which have been lost or damaged through carelessness may exceed the charges specified in the new scale; if only one lens is supplied the patient will have to pay only 10s.; in cases of carelessness the full cost of the replaced glasses (frames and lenses) will be paid by the patient.

Appeal by Institute of Psycho-Analysis

According to a recent report in the *Manchester Guardian* the Institute of Psycho-Analysis in London (at 96, Gloucester Place, W.1) is appealing for funds and hopes to raise £100,000. It was incorporated in 1924 as a place to train psycho-analysts—there are about 60 now being trained—and to hold out-patient clinics where analysts would work without fee. In addition it publishes the *International Journal of Psycho-Analysis* and maintains a good library. The clinics receive a yearly grant from the regional hospital board, but otherwise the Institute survives only on private beneficence.

Doctors Wanted in Malaya

The Secretary of State for the Colonies is appealing for doctors for Malaya, where an essential part of the re-establishment of law and order is the provision of full medical and social services. At least one year's experience after qualification is required in applicants, and secondment from the National Health Service for periods up to six years is possible. (For a definition of "secondment" see *Supplement* of May 19, p. 206.) Most men are required for general medical and health duties, including clinical teaching in the University of Malaya; there are also some vacancies for surgeons. Full information of the openings may be obtained from hospital authorities, or from the Director of Recruitment (Colonial Service), Colonial Office, Sanctuary Buildings, Great Smith Street, S.W.1.

Open Invitation from York

York Medical Society would like to meet any doctors who may be visiting York for the Festival of Britain celebrations from June 3 to 17. The society's library and house at 17, Stonygate will be open from 4 to 6 p.m. on Tuesdays, Thursdays, and Saturdays of the fortnight and members will be pleased to welcome doctors and their families for afternoon tea during that time. Tickets may be had on application at the Festival Club or to the Secretary, 17, Stonygate, York.

Ex-Minister Resumes Sanatorium Post

Dr. Noel Browne, former Irish Minister of Health, who resigned when his free Mother and Child Scheme was opposed by his Cabinet colleagues, will resume his duties as assistant resident medical superintendent at Newcastle Sanatorium, near Dublin, on June 12. He is standing as an Independent candidate in the General Election on May 30, having resigned from Mr. Sean MacBride's (External Affairs Minister) Republican Party. Dr. Browne retained his Newcastle post during his three years as Health Minister, but his duties there were carried out by a substitute.

COMING EVENTS

Institute of Urology

The Institute of Urology (University of London) in association with St. Peter's and St. Paul's Hospitals, Henrietta Street, London, W.C., has arranged a special intensive course of urological instruction to be held at the Institute from June 4 to 15, both dates inclusive. Full particulars may be obtained from the secretary of the Institute at the above address.

West London Medico-Chirurgical Society

The annual banquet of the West London Medico-Chirurgical Society will be held at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C., on Wednesday, June 6, at 7.30 for 8 p.m.

Contraceptive Technique

A lecture and demonstration (on living models) on contraceptive technique will be given by Miss Marie C. Stopes, Ph.D., at the Mothers' Clinic, 108, Whitfield Street, London, W., on Thursday, June 7, at 2.30 p.m. Tickets must be obtained in advance, as space is limited.

Maternity and Child Welfare Conference

The National Association for Maternity and Child Welfare will hold the annual conference at Church House, Westminster, on June 27, 28, and 29. It will be opened by Princess Elizabeth, and talks will be given on the present position and the objects to be achieved; the next two days will be devoted to group discussions and visits, and Mr. Hilary Marquand will close the conference. Applications for tickets (£1 1s.) should be made to the Secretary, N.A.M.C.W., 5, Tavistock Place, London, W.C.1.

Glasgow Graduates Dinner

The Glasgow Graduates Dinner will be held this year at the Mayfair Hotel, London, on June 14, at 7 for 7.30 p.m. Graduates who are unable to travel to Glasgow, but who would like to take part in the quincentenary celebrations of the University, are invited to attend the dinner. Tickets (£1 10s. exclusive of wines) may be obtained from Dr. Robert Forbes, Medical Defence Union, Tavistock House South, Tavistock Square, London, W.C.1.

Indian Medical Service Dinner

The annual dinner of the I.M.S. Dinner Club will be held at the Connaught Rooms, London, on Wednesday, June 20, at 7 for 7.30 p.m. Tickets from the Secretary, Medical Department, Commonwealth Relations Office, 4, Matthew Parker Street, S.W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

EDINBURGH UNIVERSITY.—At Physiology Class Room, May 28, 5 p.m., "*The Materialist View*," by Dr. Douglas Guthrie.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—May 28, 5 p.m., "*Ocular Palsies*," by Dr. T. Rowland Hill.

UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL, University Street, Gower Street, London, W.C.—May 28, 5.30 p.m., "*Oligophrenia Phenylpyruvica*," by Professor A. Fölling (Oslo). (See also May 29.)

Tuesday

EUGENICS SOCIETY.—At Royal Society, Burlington House, Piccadilly, London, W., May 29, 5.30 p.m., "*Recent Investigations of Intelligence and its Measurement*," by Professor P. E. Vernon, M.A., Ph.D.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—May 29, 5 p.m., "*Erythemato-Squamous Eruptions*," by Dr. H. J. Wallace.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—May 29, 5.30 p.m., "*Hormone Therapy in Ophthalmology with Cortisone and A.C.T.H.*," by Mr. H. H. Skeoch.

LONDON UNIVERSITY.—At Westminster Medical School (Meyerstein Lecture Theatre), Horseferry Road, London, S.W., May 29, 5.30 p.m., "*The Surgery of the Biliary System*," Special University Lecture by Professor Warren H. Cole (University of Illinois).

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—May 29, 5 p.m., "*Surgical Physiology of Large Arteries, with Particular Reference to Traumatic Spasm*," Arris and Gale Lecture by Mr. J. B. Kinmonth.

ST. MARY'S HOSPITAL MEDICAL SCHOOL: WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, Paddington, London, W.—May 29, 5 p.m., "*The Avoidance of Post-infection Paralyses, with Special Reference to Diphtheria Prophylaxis*," Almroth Wright Lecture by Dr. G. Bousfield.

UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL, University Street, Gower Street, London, W.C.—May 29, 5.30 p.m., "*Oligophrenia Phenylpyruvica*," by Professor A. Fölling (Oslo). (See also May 28.)

WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebone Lane, London, W.—May 29, 2.30 p.m., "*Ocular Manifestations of Nervous Diseases*," *Part I*, clinical demonstration in neurology by Mr. Joseph Minton.

Wednesday

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—May 30, 5 p.m., "*Medical Mycology—Superficial Mycotic Infections*," by Dr. R. W. Riddell.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—May 30, 5.30 p.m., "*Burns of the Eye with Reference to a Recent Form of Treatment*," by Mr. J. D. M. Cardell.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—May 30, 5.30 p.m., "*Common Plastic Operations and Orbital Surgery*," by Mr. L. H. Savin.

Thursday

EDINBURGH UNIVERSITY, University New Buildings (Anatomy Theatre), Teviot Place, Edinburgh.—May 31, 5 p.m., *"Peripheral Nerve Injuries,"* Honyman Gillespie Lecture by Mr. A. J. Slessor.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—May 31, 5 p.m., *"Seborrhoeic Dermatoses,"* by Dr. J. L. Franklin.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—May 31, 3 p.m., *"Neurosurgical Difficulties in Performing Limited Prefrontal Operations,"* Public Lecture by Dr. Jacques Le Beau (Paris).

ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Materia Medica Department, Medical School, Small's Wynd, Dundee, May 31, 5 p.m., *"Surgery of the Chronic Hip,"* by Professor W. Mercer.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—May 31, 4.30 p.m., *"Psychiatry,"* lecture-demonstration by Dr. M. A. Partridge.

UNIVERSITY COLLEGE: DEPARTMENT OF BIOCHEMISTRY, Physiology Theatre, Gower Street, London, W.C., May 31, 4.45 p.m., *"Biological Syntheses Concerning Carbohydrate Radicles,"* 2nd of four public lectures by D. J. Bell, Ph.D., Sc.D., F.R.I.C.

Friday

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—June 1, 5.30 p.m., *"Recent Advances in Pharmacology of the Eye,"* by Dr. C. A. Keele.

ROYAL SANITARY INSTITUTE.—At Guildhall, Swansea, June 1, 10 a.m., papers: *"Problems in Port Health Administration,"* by Dr. E. B. Meyrick; *"Swansea Main Drainage Scheme,"* by D. J. Milford Davies, A.M.I.Mun.E. Afternoon visits.

SOCIETY OF PUBLIC ANALYSTS: BIOLOGICAL METHODS GROUP.—At the National Institute for Medical Research, The Ridgway, Mill Hill, London, N.W., June 1, 2 p.m., summer meeting. Communications and demonstrations.

WHIPPS CROSS HOSPITAL MEDICAL SOCIETY, Whipps Cross Hospital, London, E.—June 1, 8.30 p.m., *"The Hazards of Treatment,"* by Mr. D. F. Elliison Nash.

APPOINTMENTS

BRYANT, HUGH O. M., M.B., Ch.B., D.P.H., Deputy Medical Officer of Health, County Borough of Bolton, Lancashire.

CROWLEY, ALAN F., M.B., B.Ch., Medical Officer, Wormwood Scrubs Prison, London, W.

DARKE, G. H., M.B., B.S., F.R.C.S.Ed., Consultant Surgeon to South Somerset Clinical Area (Minehead District), South-Western Regional Hospital Board. *(Corrected announcement.)*

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Davies.—On May 6, 1951, at the Maternity Home, High Wycombe, Bucks, to Mary Angela (formerly Whiteaway), wife of Dr. Leslie W. Davies, a son.

Davies.—On May 8, 1951, at Cardiff, to Marie, wife of Dr. D. M. Davies, a daughter—Siân.

Rosenvinge.—On May 7, 1951, at Carlton Lodge, Harrogate, to Margaret (formerly Ogden), wife of Dr. Gerald Rosenvinge, a sister for Louise, Stephen, and Henry—Philippa.

Smith.—On May 5, 1951, at Lincoln, to Myfanwy, wife of Dr. H. Ellis Smith, a son.

Tyrrell.—On May 13, 1951, at Hallamshire Maternity Home, to Moyra, wife of Dr. David Tyrrell, M.R.C.P., a daughter—Frances Elizabeth.

Warin.—On May 14, 1951, at St. Brenda's Nursing Home, Bristol, to Anne (formerly Hollis) and Robert Warin, M.D., M.R.C.P., a son.

Watkinson.—On May 14, 1951, at Queens Park Hospital, Blackburn, to Dr. Margaret, wife of Deryck H. Watkinson, a daughter—Deborah Jane.

MARRIAGES

Fletcher—Kent.—On May 12, 1951, at St. John's Church, Perry Barr, Birmingham, Joseph H. Fletcher, M.B., of Birmingham, to Mary Kent, M.B., of Derby.

DEATHS

Anderson.—On May 10, 1951, at Apsley Lodge, Cheltenham, Frederick Thomas Anderson, M.D., F.R.C.S.Ed., aged 88.

Bannerman.—On May 13, 1951, at The Butts House, Stanhope, Co. Durham, James Bannerman, M.B., C.M., aged 77.

Black.—On May 17, 1951, at 5, Hampton Terrace, Edinburgh, Alexander Black, M.B., Ch.B.

Bury.—On May 12, 1951, Frederick William Bury, M.D., of The Cottage, Winchelsea, Sussex, aged 79.

Cottu.—On May 9, 1951, at Worthing, Sussex, Thomas Edward Cottu, L.R.C.P.&S.I., formerly of Eastwood Lodge, Hunstanton, Norfolk.

Dudding.—On May 12, 1951, at Winteringham, Lincs, John Scarbrough Dudding, C.B., O.B.E., M.R.C.S., L.R.C.P., Surgeon Rear-Admiral, R.N., retired, aged 73.

Graham.—On May 8, 1951, Sophia Graham, M.B., B.S., D.P.M., of Riverscourt, Park Avenue, Worcester.

Hayes.—On May 18, 1951, at Kilberry, Claygate, Surrey, Arthur Herbert Hayes, F.R.C.P., D.P.H., Major, R.A.M.C., retired.

Johnston.—On May 17, 1951, William Ellis Johnston, M.B., Ch.B., of Westhoughton, Lancs, aged 45.

Johnstone.—On May 12, 1951, David Patrick Johnstone, C.I.E., O.B.E., L.R.C.P.&S.Ed., L.R.F.P.S., D.P.H., Major R.A.M.C., retired, late of Donera, Kilcoole, Wicklow.

Laird.—On April 8, 1951, Peter Alexander Laird, M.B., C.M., of "Dorema," Kilmacolm, Renfrewshire.

Mackay.—On May 18, 1951, at Norwood, Stonehaven, Kincardineshire, Alastair Frederick Buchanan Mackay, L.R.C.P.&S.Ed., L.R.F.P.S., aged 58.

Somerville-Large.—On May 1, 1951, William Collis Somerville-Large, M.B., F.R.C.S.I., of "St. Valerie," Bray, Co. Wicklow, and Dublin, Eire.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Chronic Infestation with Threadworms

Q.—*A woman, aged 37, is a chronic sufferer from threadworms. She has been treated haphazardly in the past with gentian violet, "diphenan," and acetarsol without success. She is now exceedingly worried by these constant failures to cure her. What plan of treatment is advised to eradicate the infestation once and for all? (Facilities are available for colonic irrigation if required.)*

A.—The patient should be instructed about the dangers and methods of auto-infection, and if possible she should be removed from her personal environment for the duration of the treatment. In addition to general measures to prevent reinfestation, such as scrubbing the hands, washing the perineum and buttocks on waking and after going to stool, and the wearing of suitable clothing and attention to its cleanliness, enemas of a saturated solution of hexylresorcinol may be used to kill the worms in the lower bowel. The drug may be irritating to the mucous membrane, and whether the enemas can be given daily or at less frequent intervals will have to be determined by trial. The treatment should be continued for three weeks. All other members of the family should be examined, and those found to be infected should be treated at the same time. While the patients are being treated, their rooms should be thoroughly washed and cleaned, as eggs may be found on the bedspreads, floors, and walls, and bedding and underclothes should be sterilized.

Worms from the Dog

Q.—*What intestinal parasites of the dog can infect man?*

A.—The following species of helminths occur as intestinal parasites of the dog and are also parasitic in man, but not necessarily in the human intestine nor as adult parasites. Those species which infect man only when larval or immature are marked with an asterisk. Very rare or doubtful records in either host are queried.

Roundworms: *Toxocara canis, Trichinella spiralis, Strongyloides stercoralis, Gnathostoma spinigerum,* Ankylostoma braziliense, A. caninum* (Man ?), *Necator americanus* (Dog ?), *Enterobius vermicularis* (Dog ?).

Flukes: *Heterophyes heterophyes, Metagonimus yokogawai, Monorchotrema taihokui, Echinochasmus perfoliatus, Pseudamphistomum truncatum, Schistosoma japonicum.*

Tapeworms: *Dipylidium caninum, Taenia echinococcus** (hydatid cyst in man), *T. cerebralis,* T. serialis,* Dibothriocephalus latus, D. mansoni.**

Protozoan intestinal parasites of the dog do not infect man.

Absence of the Appendix

Q.—*A man of 35 was admitted showing a classical picture of acute appendicitis. The abdomen was opened, but a thorough search did not reveal the appendix. The caecum, however, was congested (typhlitis). The abdomen was closed, and the patient's recovery was uneventful. Might this have been a case of congenital absence of the appendix?*

A.—Congenital absence of the appendix is exceptionally rare, and few authentic cases have been recorded. In the circumstances of the case described this would seem to have been an unlikely possibility. Despite the failure to find an appendix, and without any offence to the operator, one must say that this was most likely a case of acute appendicitis. It is possible for a retroperitoneal appendix, especially if

small, to be overlooked even in the course of a "cold" laparotomy. In the presence of inflammation it would be still easier for the offending organ to be missed. The fact that the patient made an uneventful recovery does not, of course, rule out the diagnosis of appendicitis. If the appendix was truly absent then it would be tempting to suggest the presence of an occult and inflamed caecal diverticulum to explain the typhlitis.

Congenital Fibrosis of the Pancreas

Q.—*What is the aetiology of congenital fibrosis of the pancreas? I have a patient who has had two children, in 1940 and 1949, with normal pregnancies and deliveries, who both died of fibrosis of the pancreas at about 6 months. The patient has just become pregnant for the third time. What are the chances of this child being affected, and are there any prophylactic measures which may be taken?*

A.—Congenital fibrosis of the pancreas is not particularly uncommon. It was first described in this country by Clarke and Hadfield in 1924 (*Quart. J. Med.*, 1924, **17**, 358), but it was not until the publication in 1938 of a series of cases by Andersen (*Amer. J. Dis. Child.*, 1938, **56**, 344) that the condition aroused the interest of paediatricians.

The disease is invariably fatal between the ages of 2 days and 14½ years. Its aetiology is unknown. The arresting lesion is a clearly defined pancreatic defect which eventually leads to pancreatic fibrosis. Two other organ defects accompany this lesion so consistently that it is almost certain they are causally linked. The first is meconium ileus producing intestinal obstruction in the newborn—this occurs in those cases in which the pancreatic lesion is far advanced at birth; the other is a pulmonary defect which terminates in chronic purulent bronchitis, bronchiectasis, and pulmonary fibrosis. The course of the disease in cases surviving for a year is almost invariably overshadowed by pulmonary suppuration, which is often staphylococcal.

The most attractive hypothesis is that the primary defect in all three situations is the production by sub-epithelial mucus glands of an abnormally viscid secretion and that this may be related to some abnormality in parasympathetic innervation. This is in all probability true of the pancreas and intestine, especially the duodenum. It is not yet fully agreed that the pulmonary suppuration is due to bronchial obstruction by an abnormally viscid bronchial mucus.

There is no question that the disease has a highly significant hereditary background due to a single recessive lethal gene which in the pure or homozygous state is causally linked with the organ defects. Direct transmission and the existence of a single Mendelian dominant can be ruled out. Consanguinity in the parents is very uncommon, strongly suggesting that the gene is not a particularly rare one. It has been found that the disease was present in 12 children out of 6,500 admissions, and in approximately 4% of a large series of necropsies in a children's hospital. The transmission is not sex-linked, as there is no sex predominance, and in the large majority of cases there are no other congenital abnormalities. It bears no relation to birth order, and cannot therefore be related to the age of the mother.

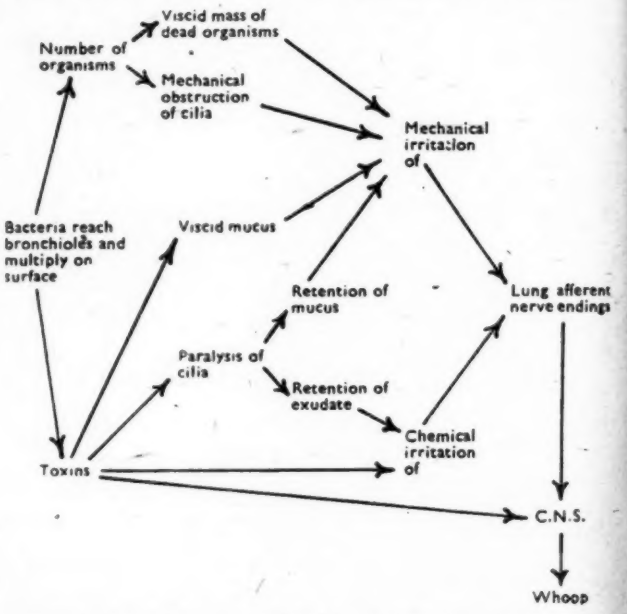
With this well-defined hereditary background it can be stated with certainty that the chances that the next child will suffer from the disease are precisely one out of four. Prognosis is clearly related to the *severity* of the pulmonary disease, and not necessarily to the time of onset of pulmonary symptoms.

No suggestions have yet been made about prophylaxis.

The Whoop in Whooping-cough

Q.—*Does Haemophilus pertussis have any toxic action on the cilia of the respiratory tract? I have heard that in whooping-cough the cilia are paralysed.*

A.—There is no direct evidence that *Haemophilus pertussis* has any specific paralysing or destructive action on cilia. In 1912 Mallory and Hornor[1] found masses of Gram-negative organisms, indistinguishable from *H. pertussis*, among the cilia of cells lining the trachea, bronchi, and bronchioles of children dying of whooping-cough. Organisms were crowded even between the stumps of cilia and in mucus overlying epithelium denuded of cilia. Mallory and Hornor thought that the bacteria mechanically obstructed the cilia and possibly led to their destruction. The whoop would thus be due to the local irritation of stagnant mucus and inflammatory exudate. Few now believe this to be the whole truth. Experimental infection provokes a spasmodic cough only in the human,[2] ape,[3 4] and possibly monkey.[5 6] But the histological changes of pertussis are neither specific nor confined to man. They occur in other bacterial and viral infections of the lung, and can be produced by the inoculation of living *H. pertussis* in apes, monkeys, cotton rats, mice,[7] and chick



embryo.[8] Lung sections of all these animals show masses of organisms among the cilia, a mixed mono- and polymorphonuclear exudate in the alveoli, superficial inflammation of the mucosa, desquamation of epithelium, patchy interstitial pneumonitis, and, in the later stages, obstructive emphysema and atelectasis. The mechanism of the whoop in humans is unknown. Above is a schematic representation of conceivable theories of the pathogenesis of the whoop in whooping-cough; only further work will settle which is correct.

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Correction.—In the paper by Drs. J. B. Enticknap and B. J. Stephens on "Laboratory Diagnosis of Urinary-tract Infections" (May 19, p. 1119) a mistake arose from a transposed heading on p. 1121. Under the heading "Haemolysin; Gelatin Liquefaction" the statement is made in the second paragraph: "Only five strains possessed this ability, and none of them was a true *Bact. cloacae* strain." This statement should refer only to gelatin liquefaction.

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